

**REMARKS**

This paper is being filed in response to the Office Action dated November 7, 2002 that was issued in connection with the above-identified patent application. Applicants request a one-month extension of time and enclose the fee required pursuant to 37 C.F.R. §1.17(a)(1). Applicants also enclose herewith a Supplemental Information Disclosure Statement, Form PTO-1449, and the fee required pursuant to 37 C.F.R. §§1.17(p) and 1.97(c). Applicants respectfully request reconsideration of the instant application in view of the amendments and remarks presented herein.

Claims 39-86 are pending. Claims 52, 57-79, 80-81, and 83-84 have been withdrawn from consideration. Claims 39-41, 52, 54, 57-79, 80-81, and 83-84 have been cancelled herein without prejudice and Claims 42-49, 53, 55-56, 82, and 85-86 have been amended. The amendments are supported by the instant specification and, therefore, do not constitute new matter. Upon entry of the instant Amendment, claims 42-51, 53, 55-56, 82, and 85-86 will be pending.

Rewritten specification paragraphs and claims appear in the preceding "IN THE SPECIFICATION" and "IN THE CLAIMS" sections respectively. Attached hereto is a marked-up version of the changes made by the instant amendment. The attached pages are captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE" and are included pursuant to 37 C.F.R. §1.121(c)(ii). Should any discrepancies be discovered, the version presented in the preceding "IN THE SPECIFICATION" and "IN THE CLAIMS" sections shall take precedence.

**Clarification of Species Elected**

During a telephone conference with the Examiner on August 16, 2002, Applicant's Attorney, Rochelle K. Seide, attempted to communicate to the Examiner that a species election of a group of individual nucleic acid sequences consisting of SEQ ID NOS:1, 3, and 5 was preferred. Evidently, however, the Examiner had a different understanding of a species election of a combination of SEQ ID NOS:1, 3, and 5. Applicant's Agent, Guy Birkenmeier, had a telephone conversation with the Examiner on January 28, 2003 wherein the Examiner indicated that she would permit Applicants to shift their species election to a single sequence of SEQ ID NOS:1, 3 and 5. Applicants thank the Examiner for granting this request and elect SEQ ID NO:3 (and the encoded polypeptide, SEQ ID NO:4) as the species for further consideration.

**Sequence Letter**

The Examiner has objected to the specification as containing sequence disclosures, yet allegedly failing to comply with 37 C.F.R. §§1.821-1.825. Applicants traverse this objection and assert that the specification, as amended by Applicant's Preliminary Amendment filed on March 5, 2002, complies with 37 C.F.R. §§1.821-1.825. Applicants enclose a copy of that Preliminary Amendment together with a copy of Applicant's Return Postcard. Applicants respectfully request consideration and entry of their March 5, 2002 Preliminary Amendment. Applicants, therefore, respectfully request withdrawal of the instant objection.

### **Drawings**

The Examiner has objected to the drawings on the grounds that the Brief Description of the Drawings allegedly fails to refer to multiple frames. Applicants assert that the Brief Description of the Drawings, as amended herein, fully complies with MPEP §608.01(f) and, therefore, respectfully request withdrawal of this objection.

### **Claims Are Draw to Statutory Subject Matter**

The Examiner has rejected claims 39-42, 45-47, and 55-56 under 35 U.S.C. §101 as allegedly reading on a product of nature.

Claims 39-41 have been cancelled rendering rejection of these claims moot. Applicants traverse this rejection with respect to the remaining claims and assert that the claims are drawn to statutory subject matter. Applicants assert that it is unnecessary to recite "isolated" or "purified" in the instant claims because a polypeptide having the amino acid sequence of SEQ ID NO:4 and nucleic acids which encode such a polypeptide do not occur in nature. *See e.g.* Example 7 and Figures 2A and 2B. Since the engineered molecules having the sequences of SEQ ID NOS:3 and 4 respectively display the requisite "hand of man", Applicants respectfully request withdrawal of this rejection.

The Examiner has also rejected claims 48-51 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph as allegedly unsupported by a specific and substantial asserted utility or a well established utility.

Applicants traverse this rejection and assert that the claims, as amended herein, are drawn to statutory subject matter having specific, substantial, and credible utility. The risks and consequences of human exposure to botulinum neurotoxin are readily apparent to those of

ordinary skill in the art and, indeed, to society at large. Applicants assert that the nucleic acids, the polypeptides, and the methods of the invention have use, *inter alia*, in immunization of humans and mammals against botulinum neurotoxin toxicity. *See e.g.* Example 10, page 41, lines 8-24 and Table 6. Therefore, Applicants respectfully request withdrawal of these rejections.

**Claims Are Supported by Sufficient Description**

Claims 39-42, 44-51, 55-56, 82, and 85-86 have been rejected under 35 U.S.C. §112, first paragraph as allegedly lacking sufficient description to convey to one skilled in the art that Applicants were in possession of the invention at the time of filing. The Examiner has alleged that the description does not support the breadth of claims drawn to a genus of nucleic acids where only one species is provided and the claim(s) do not recite a specific function of the nucleic acids.

Claims 39-41 have been cancelled rendering rejection of these claims moot. Applicants traverse this rejection with respect to the remaining claims and assert that the claims, as amended herein, are fully supported by the description such that one of ordinary skill in the art would readily appreciate that Applicants were in possession of the invention on or before the filing date. Claim 43 has been amended to independent form. Support for this amendment may be found in the specification as filed at, *inter alia*, Example 7 and Figure 2. Therefore, Applicants respectfully request withdrawal of this rejection.

**Claims Are Not Drawn to New Matter**

Claims 39-42, 44-51, 55-56, 82, and 85-86 have been rejected under 35 U.S.C. §112, first paragraph as drawn to subject matter that allegedly is not described in the specification in such a way as to convey to one skilled in the art that applicants had possession of an invention constituting a single nucleic acid that is a combination of SEQ ID NOS:1, 3, and 5.

Claims 39-41 have been cancelled rendering rejection of these claims moot. Applicants assert that this rejection is also moot with respect to the remaining claims since none of these claims, as amended herein, recite "combinations thereof". This amendment to the claims has been made pursuant to the telephone conversation with Applicant's Agent Guy Birkenmeier on January 28, 2003, wherein the Examiner kindly granted Applicant's request to shift their species election to SEQ ID NOS:3 and 4. Therefore, respectfully request withdrawal of this rejection.

**Claims Are Enabled by the Description**

Claim 54 has been rejected under 35 U.S.C. §112, first paragraph as drawn to subject matter that allegedly is not described in the specification in such a way as to enable one skilled in the art to make and use the invention. The Examiner has alleged that the recombinant organism of claim 54 does not produce, express, or comprise a coding sequence for botulinum neurotoxin.

Claim 54 has been cancelled. Applicant's response to this rejection is directed to claim 53. Applicants traverse this rejection and assert that claim 53, as amended herein, is fully enabled by the specification as filed. The transfected cell of claim 53 comprises "an expression

vector comprising a nucleic acid having a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:4." Moreover, the method of claim 53 comprises culturing this organism "under conditions wherein the nucleic acid is expressed". This claim has ample support in the specification at, *inter alia*, Examples 3 and 8. Therefore, Applicants respectfully request withdrawal of this rejection.

**Claims Are Clear and Definite**

Claims 39-42, 44--51, 53-56, 82, 85, and 86 have been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly reciting non-elected inventions. Claims 39-41 have been cancelled rendering rejection of these claims moot. Applicants assert that the remaining claims, as amended herein, do not recited non-elected subject matter.

Claims 39-41 have been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for use of the phrases "encodes the carboxy-terminal portion" (claim 39), "is capable of" (claim 39), "the gram negative bacteria is Escherichia coli" (claim 40), and "the yeast is Pichia pastoris". Applicants respectfully submit that these rejections are moot since, as noted above, claims 39-41 have been cancelled.

Claim 44 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "wherein the nucleic acid is a synthetic nucleic acid". Claim 44, as amended herein; does not recite this phrase.

Claims 45 and 46 have been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly lacking antecedent basis for the recited expression control sequence. Applicants have amended claim 45 to recite "further comprising" according to the Examiner's suggestion.

Claim 48 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the word "organism" in reference to mammalian cell lines. Claim 48 has been amended herein to replace the word "organism" with the word "cell".

Claim 48 has also been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "transfecting an organism with the nucleic acid of claim 39". The Examiner has alleged that the nucleic acid of claim 39 is defined as any portion of the carboxy-terminus of botulinum neurotoxin heavy chain and therefore, is not required to encode a botulinum neurotoxin. The Examiner has requested clarification as to what is encoded by the nucleic acid and what is expressed therefrom.

Applicants traverse this rejection and assert that claim 48, as amended herein, clearly sets forth what is encoded by the nucleic acid and what is expressed therefrom. Applicants respectfully invite the Examiner's attention to the phrase "a nucleic acid having a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:4" in relation to what is encoded by the nucleic acid. In addition, Applicants respectfully invite the Examiner's attention to the phrase "comprising at least one immunogenic epitope" in relation to what is expressed. Applicants assert that one of ordinary skill in the art would recognize that while all or substantially all of the nucleic acid may be expressed by the recombinant cell of claim 48, the polypeptide comprising a carboxy-terminal portion of the heavy chain of botulinum neurotoxin serotype a comprising at least one immunogenic epitope constitutes less than the full-length of SEQ ID NO:4. In view of these and other amendments, Applicants assert that claim 48 is clear and definite.

Claim 49 has been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly lacking antecedent basis for the term "protein". The Examiner has alleged that it is

unclear whether the carboxy-terminal is a part of the "protein". The Examiner has also alleged that it is unclear what "protein" is being recovered. Applicants traverse this rejection and assert that claim 49, as amended herein, satisfies the requirements of 35 U.S.C. §112, second paragraph.

Claim 53 has been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly failing to recite method steps that correspond with the preamble. The Examiner has alleged that claim 53 fails to recite expression or isolation of a heavy chain portion or preparation or formulation of an immunogenic composition. Claim 53 has also been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "in expressible form".

Applicants traverse this rejection and assert that claim 53, as amended herein, claims the subject method in a manner that complies with 35 U.S.C. §112, second paragraph. Applicants respectfully invite the Examiner's attention to the phrase "recovering from said transfected cell at least one insoluble polypeptide" recited by amended claim 53. In view of this phrase and other amendments, Applicants assert that the method steps of amended claim 53 correspond to the preamble. In addition, amended claim 53 does not recite the phrase "in expressible form".

Claim 54 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "recovering an insoluble protein fraction". This rejection will be moot upon entry of the instant Amendment whereby claim 54 has been cancelled.

Claims 85 and 86 have been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly lacking antecedent basis for the term "protein". Claims 85 and 86 have been amended to recite "polypeptide" as is clearly recited in amended claim 43.



For the foregoing reasons, Applicants believe that the claims comply with the requirements of 35 U.S.C. §112, second paragraph and, therefore, respectfully request withdrawal of these rejections.

**Claims Are Novel over the Cited Documents**

Claims 43, 48, and 53 are independent claims. Claims 42, 44-47, 55-56, 82, and 85-86 depend from claim 43. Claims 49-51 depend from claim 48. For a reference to anticipate, it must teach each and every element of the subject claim. *See e.g.* MPEP §2131. Since a dependent claim is to be construed to include all of the limitations of the claim from which it depends, *see e.g.* 37 C.F.R. §1.75(c), a document that fails to teach an element of an independent claim necessarily fails to teach an element of an attendant dependent claim. Therefore, Applicants will respond to the following rejections primarily as they apply to claims 43, 48, and 53.

**1. Smith 1998 Does Not Teach SEQ ID NO:4**

Claims 39, 41, 48, and 51 have been rejected under 35 U.S.C. §102(a) as allegedly unpatentable over Smith LA, 1998, *Toxicon* 36(11):1539-1548 (hereinafter “Smith 1998”). The Examiner has alleged that Smith 1998 discloses a nucleic acid encoding a *Clostridium botulinum* type A heavy chain capable of being expressed in *Pichia pastoris*. The Examiner has further alleged that Smith 1998 discloses a method of producing an immunogenic composition comprising culturing a recombinant *Pichia pastoris* cell and recovering the expressed heavy chain polypeptide.

Claims 39 and 41 have been cancelled rendering rejection of these claims moot. Applicants traverse this rejection with respect to the remaining claims and assert that Smith 1998

does not anticipate the claimed invention. Claim 48, as amended herein, recites “transfecting a cell with a nucleic acid having a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:4, said amino acid sequence comprising at least one immunogenic epitope”. Smith 1998 teaches neither the amino acid sequence of SEQ ID NO:4 nor the nucleic acid sequence of SEQ ID NO:3 (claim 42). Since Smith 1998 does not teach each and every element of the claimed invention, Applicants respectfully request withdrawal of this rejection.

## **2. Halpern Does Not Teach SEQ ID NO:4**

Claims 39-47, 54-56, 82, and 85-86 have been rejected under 35 U.S.C. §102(a) as allegedly unpatentable over Halpern JL et al., 1993, *J. Biol. Chem.* 268(15):11188-11192 (hereinafter “Halpern”). The Examiner has alleged that Halpern discloses a nucleic acid that has a nucleotide sequence encoding the carboxy-terminal portion of a botulinum neurotoxin, wherein the nucleic acid encodes an amino acid sequence that is conserved across Clostridial neurotoxins. The Examiner has further alleged that Halpern discloses a nucleic acid encoding the amino acid sequence Asp-Glu-Gly-Trp-Thr. In addition, Halpern allegedly discloses antibody and immunogenic composition preparation and nucleic acid expression with a T7 RNA polymerase promoter. It also has been alleged that Halpern discloses expression of the nucleic acids of Halpern in recombinant mammalian host cells as well as recovery of the expressed protein.

Claims 39-41, 54 and 83-84 have been cancelled rendering rejection of these claims moot.

Applicants traverse this rejection with respect to the remaining claims and assert that the claims, as amended herein, are not anticipated by Halpern. Claims 43 and 53 each recite a "a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:4, said amino acid sequence comprising at least one immunogenic epitope". Applicants

respectfully invite the Examiner's attention to Alignment 1 attached hereto which shows that the sequence of Halpern is not the same as the polypeptide sequence of SEQ ID NO:4 of the present invention. Therefore, since Halpern fails to teach Smith SEQ ID NO:4, Halpern fails anticipate each and every element of claims 43 and 53. Consequently, Applicants respectfully request withdrawal of this rejection.

### **3. Kink Does Not Teach SEQ ID NO:4**

Claims 39-42, 44-51, 55-56, 82, and 85-86 have been rejected under 35 U.S.C. §102(b) as allegedly unpatentable over U.S. Pat. No. 5,736,139 to Kink et al. issued April 7, 1998 (hereinafter "Kink"). Kink allegedly discloses a nucleic acid which encodes a portion of the carboxy-terminal portion of the heavy chain of botulinum neurotoxin. The Examiner has alleged that the nucleic acid of Kink shares certain percentages of sequence identity over portions of SEQ ID NOS:1, 3, and 5. It has also been alleged that the nucleic acid of Kink was introduced into *E. coli* and expressed as a polypeptide.

Claims 39-41, 54 and 83-84 have been cancelled rendering rejection of these claims moot.

Applicants traverse this rejection with respect to the remaining claims and assert that the claims, as amended herein, are not anticipated by Kink. Claims 43, 48, and 53 each recite a "a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:4, said amino acid sequence comprising at least one immunogenic epitope". Applicants respectfully invite the Examiner's attention to Alignments 2 and 3 attached hereto, which show that SEQ ID NO:22 of Kink is not the same as SEQ ID NOS:3 and 4 of the present invention. Therefore, since Kink fails to teach Smith SEQ ID NO:4, Kink fails anticipate each and every

element of claims 43, 48, and 53. Consequently, Applicants respectfully request withdrawal of this rejection.

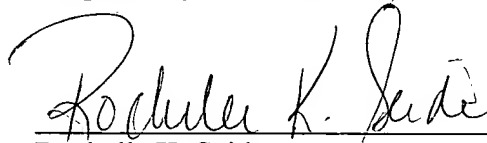
In conclusion, claims 42-51, 53, 55-56, 82, and 85-86 are drawn to statutory subject matter, recite language that complies with 35 U.S.C. §112, and are not anticipated by any of the asserted documents. Therefore, Applicants believe this application is in condition for allowance and respectfully request issuance of a Notice of Allowance.

Applicants note that the Office Action dated November 7, 2002 included several sequence alignments. However, Applicants found it difficult to interpret these alignments due to the absence of meaningful labels and/or the poor quality of the photocopies provided. Therefore, should the Examiner continue to maintain any of the foregoing art rejections, Applicants respectfully request new alignments with clear labels identifying which invention sequence is aligned with which sequence of the asserted art.

Applicants request a one-month extension of time and enclose the fee required pursuant to 37 C.F.R. §1.17(a)(1). Applicants also enclose the fee required pursuant to 37 C.F.R. §1.17(p) and 1.97(c). Applicants do not believe that any additional fees are due with this submission. Nevertheless, the Commissioner is hereby authorized to charge any fees due with this submission not otherwise enclosed herewith to Deposit Account No. 02-4377. Please credit any overpayment of fees associated with this filing to the above-identified deposit account. A duplicate of this page is enclosed. A copy of the Notice to Comply is also enclosed.

March 7, 2003

Respectfully submitted,



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Enclosures

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

This marked-up version was prepared with DeltaView software (v2.7). In this section, added text is marked with double underlining. *e.g.* added text, and deleted text is marked by a single strikethrough, *e.g.* ~~deleted text~~.

**IN THE SPECIFICATION**

The paragraphs beginning at page 6, line 20 and ending at page 6, line 32 have been **amended** as follows:

~~It is an object of this~~The instant invention ~~to~~  
~~provide~~provides immunogenic peptides capable of eliciting  
protective immunity against botulinum neurotoxin of  
serotypes A-G.

~~It is another object of this~~The instant invention  
~~to~~also provideprovides vaccines capable of eliciting  
protective immunity against botulinum neurotoxin, where the  
vaccines do not act as neurotoxins themselves.

~~It is yet another object of this~~The instant  
invention ~~to~~further provideprovides methods for preparing  
non-toxic peptides for use in vaccines against botulinum  
neurotoxin by growing recombinant organisms which express  
the peptides.

~~It is still another object of this~~The instant  
invention ~~tealso provide~~provides methods for fast and  
efficient purification of the non-toxic peptides from  
cultures of recombinant organisms.

These and other ~~objects~~aspects are ~~met~~illustrated  
by one or more of the following embodiments of the present  
invention.

The paragraphs beginning at page 9, line 20 and ending at page 11, line 12 have  
been **amended** as follows:

~~Figure 1 shows the~~Figures 1A and 1B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype A (SEQ ID NOS:1 ~~and the encoded amino acids~~  
~~sequence2~~).

~~Figure 2 shows the~~Figures 2A and 2B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype A (SEQ ID NOS:3 ~~and the encoded amino acids~~  
~~sequence4~~).

~~Figure 3 shows the~~Figures 3A and 3B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype A (SEQ ID NOS:5 and ~~the encoded amino acids~~  
~~sequence~~6).

~~Figure 4 shows the~~Figures 4A and 4B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype B (SEQ ID NOS:7 and ~~the encoded amino acids~~  
~~sequence~~8).

~~Figure 5 shows the~~Figures 5A and 5B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype C (SEQ ID NOS:9 and ~~the encoded amino acids~~  
~~sequence~~10).

~~Figure 6 shows the~~Figures 6A and 6B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype D (SEQ ID NOS:11 and ~~the encoded amino acids~~  
~~sequence~~12).

~~Figure 7 shows the~~Figures 7A and 7B respectively  
show the nucleotide sequence and the encoded amino acid



sequence for a synthetic gene encoding the H<sub>c</sub> fragment of BoNT serotype E (SEQ ID NOS:13 and ~~the encoded amino acids sequence~~14).

Figure 8 shows the nucleotide sequence for a synthetic gene encoding the H<sub>c</sub> fragment of BoNT serotype E and the encoded amino ~~acids~~acid sequence (SEQ ID NOS:35 and 36).

~~Figure 9 shows the~~Figures 9A and 9B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of BoNT serotype F (SEQ ID NOS:15 and ~~the encoded amino acids sequence~~16).

~~Figure 10 shows the~~Figures 10A and 10B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>c</sub> fragment of BoNT serotype G (SEQ ID NOS:17 and ~~the encoded amino acids sequence~~18).

~~Figure 11 shows the~~Figures 11A and 11B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>N</sub> fragment of BoNT serotype A (SEQ ID NOS:19 and ~~the encoded amino acids sequence~~20).

~~Figure 12 shows the~~Figures 12A and 12B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>N</sub>  
fragment of BoNT serotype B (SEQ ID NOS:21 and ~~the encoded~~  
~~amino acids sequence~~22).

~~Figure 13 shows the~~Figures 13A and 13B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>N</sub>  
fragment of BoNT serotype C (SEQ ID NOS:23 and ~~the encoded~~  
~~amino acids sequence~~24).

~~Figure 14 shows the~~Figures 14A and 14B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>N</sub>  
fragment of BoNT serotype D (SEQ ID NOS:25 and ~~the encoded~~  
~~amino acids sequence~~26).

~~Figure 15 shows the~~Figures 15A and 15B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>N</sub>  
fragment of BoNT serotype E (SEQ ID NOS:27 and ~~the encoded~~  
~~amino acids sequence~~28).

~~Figure 16 shows the~~Figures 16A and 16B  
respectively show the nucleotide sequence and the encoded

amino acid sequence for a synthetic gene encoding the H<sub>N</sub> fragment of BoNT serotype F (SEQ ID NOS:29 and ~~the encoded amino acids sequence~~30).

~~Figure 17 shows the~~Figures 17A and 17B respectively show the nucleotide sequence and the encoded amino acid sequence for a synthetic gene encoding the H<sub>N</sub> fragment of BoNT serotype G (SEQ ID NOS:31 and ~~the encoded amino acids sequence~~32).

~~Figure 18 shows the~~Figures 18A and 18B respectively show the nucleotide sequence and the encoded amino acid sequence for a synthetic gene encoding the H<sub>C</sub> fragment of BoNT serotype F (SEQ ID NOS:33 and ~~the encoded amino acids sequence~~34).

Figures 19A, 19B, and 19C. Figure 19A shows ~~(A)the~~ AT base content of a putative fragment C region in native *C. botulinum* DNA. ~~(Figure 19B) Reduction at~~ shows the reduced AT content after the first design (rBoNTF(Hc)1) of the synthetic gene. ~~(Figure 19C) shows the~~ AT content of the final gene design (rBoNTF(Hc)2) used to express recombinant rBoNTF(Hc) in *P. pastoris*.

Figures 20A and 20B. Figure 20A shows ~~(A)an~~ SDS-PAGE gel and ~~(Figure 20B) shows a~~ Western blot of samples

at various steps along the rBoNTF(Hc) purification. Lanes from both figures are identical except lane 1, where SDS-PAGE shows Novex mark 12 wide-range molecular weight markers and Western blot shows Novex See Blue prestained molecular weight markers. Lane 2 is the cell lysate, lane 3 is the cell extract, lane 4 is the cell extract after dialysis, lane 5 is pool of rBoNTF(Hc) positive fractions after Mono S column chromatography, and lane 6 is pool of rBoNTF(Hc)-positive fractions after hydrophobic interaction chromatography.

~~Figure~~Figures 21A and 21B show purification of rBoNTF(Hc) by sequential chromatography. ~~(Figure 21A)~~ shows Mono S cation exchange chromatography of extract from *P. pastoris*. Proteins were eluted with increasing NaCl gradient. Fractions positive for rBoNTF(Hc) by Western analysis were pooled individually and subjected to hydrophobic interaction chromatography (the results of which are shown in Figure 21B) and proteins were eluted with a decreasing ammonium sulfate gradient. In both panels, protein monitored by A280nm is recorded on the left axis and elution conditions are recorded on the right axis, with the gradient trace laid over the chromatogram.

IN THE CLAIMS

Claims 42-49, 53, 55-56, 82, and 85-86 have been **amended** as follows:

42. (AMENDED) The nucleic acid of claim ~~39~~, 43, wherein said ~~nucleic acid comprises the nucleic acid~~nucleotide sequence is nucleotides 13-1314 of SEQ ID No. ~~1~~, SEQ ID No. ~~3~~, SEQ ID No. ~~5~~, or combinations thereof. NO:3.
43. (AMENDED) A nucleic acid ~~comprising~~having a nucleotide sequence which encodesencoding a polypeptide ~~having~~comprising the amino acid sequence of SEQ ID No. ~~2~~, SEQ ID No. NO:4, SEQ ID No. ~~6~~, or combinations thereof said amino acid sequence comprising at least one immunogenic epitope.
44. (AMENDED) The nucleic acid of claim ~~39~~, 43, wherein said nucleic acid is an ~~synthetic~~isolated nucleic acid.
45. (AMENDED) The nucleic acid of claim ~~39~~, wherein ~~said nucleic acid is operably linked to~~43 further comprising an expression control ~~sequence~~sequence operably linked to said nucleotide sequence.

46. (AMENDED) The nucleic acid of claim ~~39,45,~~ wherein said expression control ~~sequences~~sequence ~~comprise~~comprises a promoter.
47. (AMENDED) The nucleic acid of claim ~~39,45,~~ wherein said expression control ~~sequences~~sequence ~~comprise~~comprises an enhancer.
48. (AMENDED) A method of preparing a polypeptide comprising ~~thea~~a carboxy-terminal portion of the heavy chain of botulinum neurotoxin serotype A comprising at least one immunogenic epitope, ~~said method comprising:~~
- transfecting ~~an-organisma~~a cell with ~~thea~~a nucleic acid having a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of elaim-39,SEQ ID NO:4, said amino acid sequence comprising at least one immunogenic epitope; and
- culturing the transfected ~~organism~~cell under conditions wherein the ~~carboxy-terminal portion of the heavy chain of botulinum neurotoxin serotype A~~nucleic acid is expressed,
- wherein the ~~organism~~cell is selected from the group consisting of a gram negative bacteria, a yeast, and a mammalian cell~~-line~~.

49. (AMENDED) The method of claim 48, further comprising recovering ~~insoluble protein from~~ said transfected ~~organism~~cell at least one insoluble polypeptide having the amino acid sequence of SEQ ID NO:4, said amino acid sequence comprising at least one immunogenic epitope.

53. (AMENDED) A method of preparing ~~the an~~an immunogenic composition comprising a polypeptide having the amino acid sequence of claim 52, SEQ ID NO:4, said method~~amino acid sequence comprising at least one immunogenic epitope, comprising :~~

culturing a ~~recombinant host organism~~cell transfected with an expression vector comprising a nucleic acid comprising a nucleotide sequence encoding, in an expressable form, a polypeptide comprising the carboxy terminal portion~~amino acid sequence of SEQ ID NO:4, said amino acid sequence comprising at least one immunogenic epitope under conditions wherein the heavy chain of botulinum neurotoxin serotype A.~~nucleic acid is expressed;  
and

recovering from said transfected cell at least one insoluble polypeptide comprising the amino acid

sequence of SEQ ID NO:4, said amino acid sequence  
comprising at least one immunogenic epitope,

wherein the cell is selected from the group consisting  
of a gram negative bacteria, a yeast, and a mammalian  
cell.

55. (AMENDED) The nucleic acid of claim ~~39~~43, wherein the A+TAT content is less than about 70% of the total base composition.
56. (AMENDED) The nucleic acid of claim 55, wherein the A+TAT content is less than about 60% of the total base composition.
82. (AMENDED) A recombinant host cell comprising the nucleic acid of claim ~~39~~45.
85. (AMENDED) The recombinant host cell of claim 82, wherein said ~~protein~~polypeptide is at least 0.75% (w/w) of the total cellular protein.
86. (AMENDED) The recombinant host cell of claim 85, wherein said ~~protein~~polypeptide is at least 20% (w/w) of the total cellular protein.



# Alignment 1

Smith SEQ ID NO:4 (hereinafter "Smith4\_419") was aligned with the amino acid sequence of Halpern (as shown at p. 11189, col. 1, paragraph 4, line 2; hereinafter "Halpern"). Identical amino acids are marked by an asterix highlighted in yellow.

Smith4_419	MSTFTEYIKNIINTSILNLRYESNHLIDLRYASKINIGSKVNFDPIDKNQIQLFNLESSKIEVILKNAIVYNSMYENFSTSFWIRIPKYFNSISLNNEYTIINC MENNSGWKVSLNYGE
Halpern	-----
Smith4_419	IIWTLQDTQEIKQRVVFYKYSQMINISDYINRWIPVTITNNRLNNSKIYINGRLIDQKPISNLGNIHASNNIMFKLDGCRDTHRYIWIKYFNLFDKELNEKEIKDLYDNQNSGILKDFWG
Halpern	-----
Smith4_419	DYLQYDKPYMYMLNLYDPNKVVDVNNVGIRGYMYLKGPRGSVMTTNIYLNSSLYRGTKPIIKKYASGNKDNIVRNDRVYINVVVKNEYRLATNASQAGVEKILSALEIPDVGNLSQVVV
Halpern	-----
Smith4_419	MKSKNDQGITNKCKMNLQDNNGNDIGFIGFHQFNNAKLVASNWNQIERSSRTLGCSEWEIFPVDDGWERPL
Halpern	-----CDKILGCDWYFVPTDEGWT-----
	*** * * * *

**Alignment 2**

Smith SEQ ID NO:3 (hereinafter "Smith3\_419") was aligned with the nucleotide sequence of SEQ ID NO:22 of Kink (U.S. Pat. No. 5,736,139; hereinafter "Kink22\_139"). The coding sequence of the respective nucleic acids is shown in blue. Identical nucleotides are marked by an asterix highlighted in yellow.

```
Smith3_419      GAAATCGAAACGATG-----TCTACCTTCACTGAATACATCAAGAACAATCATCAATACCTCCAATCTGAACCTGCGCTACGAATCCAATCACCTGATCGACCTGTCTCGCTAC
Kink22_139      -----ATGGCTCGTCTGCTGTCTACCTTCACTGAATACATCAAGAACAATCATCAATACCTCCAATCTGAACCTGCGCTACGAATCCAATCACCTGATCGACCTGTCTCGCTAC
                ***
Smith3_419      GCTTCCAAAAATCAACATCGGTTCTAAAGTTAACTTCGATCCGATCGACAAGAATCAGATCCAGCTGTTCATCTGGAATCTTCCAAAAATCGAAGTTATCCCTGAAGAATGCTATCGTATAC
Kink22_139      GCTTCCAAAAATCAACATCGGTTCTAAAGTTAACTTCGATCCGATCGACAAGAATCAGATCCAGCTGTTCATCTGGAATCTTCCAAAAATCGAAGTTATCCCTGAAGAATGCTATCGTATAC
                *****
Smith3_419      AACTCTATGTACGAAAACCTTCTCCACCTCCCTTCTGGATCCGTATCCCGAAATACTTCAACTCCAATCTCTCTGAACAAATGAATACACCATCATCAACTGCATGGAAAAACAAATCTGGTTGG
Kink22_139      AACTCTATGTACGAAAACCTTCTCCACCTCCCTTCTGGATCCGTATCCCGAAATACTTCAACTCCAATCTCTCTGAACAAATGAATACACCATCATCAACTGCATGGAAAAACAAATCTGGTTGG
                *****
Smith3_419      AAAGTATCTCTGAATACCGTGAATATCATCTGGACTCTGCAGGACACTCAGGAAATCAAAACAGCGTGTGTATTTCAAACTACTCTCAGATGATCAACATCTCTGACTACATCAATCGCTGG
Kink22_139      AAAGTATCTCTGAATACCGTGAATATCATCTGGACTCTGCAGGACACTCAGGAAATCAAAACAGCGTGTGTATTTCAAACTACTCTCAGATGATCAACATCTCTGACTACATCAATCGCTGG
                *****
Smith3_419      ATCTTCGTTCACCATCAACAAATCGTCTGAATAACTCCAAAAATCTACATCAACGGCCGTCTGATCGACCAGAAACCGATCTCCAATCTGGGTAACATCCACGCTTCTAAATACATCATG
Kink22_139      ATCTTCGTTCACCATCAACAAATCGTCTGAATAACTCCAAAAATCTACATCAACGGCCGTCTGATCGACCAGAAACCGATCTCCAATCTGGGTAACATCCACGCTTCTAAATACATCATG
                *****
Smith3_419      TTCAAACCTGACGGTGTCTGTGACACTCACCGCTACATCTGGATCAAACTTCAATCTGTTCGACAAAGAACTGAACGAAAAAGAAATCAAGACCTGTACGACAACAGTCCAATTTCT
Kink22_139      TTCAAACCTGACGGTGTCTGTGACACTCACCGCTACATCTGGATCAAACTTCAATCTGTTCGACAAAGAACTGAACGAAAAAGAAATCAAGACCTGTACGACAACAGTCCAATTTCT
                *****
Smith3_419      GGTATCTCTGAAAGACTTCTGGGGTGACTACCTGCAGTACGACAAACCGTACTACATGCTGAATCTGTACGATCCGAAACAAATACGTTGACGTCAACAAATGTAGGTATCCCGGGTTACATG
Kink22_139      GGTATCTCTGAAAGACTTCTGGGGTGACTACCTGCAGTACGACAAACCGTACTACATGCTGAATCTGTACGATCCGAAACAAATACGTTGACGTCAACAAATGTAGGTATCCCGGGTTACATG
                *****
Smith3_419      TACCTGAAAGGTCCGGTGGTTCTGTATGACTACCAACATCTACCTGAATCTTCCCTGTACCGTGGTACCAAAATTCATCATCAAGAAATACCGCTCTGGTAACAAGGACAAATATCGTT
Kink22_139      TACCTGAAAGGTCCGGTGGTTCTGTATGACTACCAACATCTACCTGAATCTTCCCTGTACCGTGGTACCAAAATTCATCATCAAGAAATACCGCTCTGGTAACAAGGACAAATATCGTT
                *****
Smith3_419      CGCAACAAATGATCGTGATACATCAATGTGTAGTTAAGAACAAGAAATACCGTCTGGCTACCAATGCTTCTCAGGCTGGTGTAGAAAAGATCTTGTCTGCTCTGGAAATCCCGGACGTT
Kink22_139      CGCAACAAATGATCGTGATACATCAATGTGTAGTTAAGAACAAGAAATACCGTCTGGCTACCAATGCTTCTCAGGCTGGTGTAGAAAAGATCTTGTCTGCTCTGGAAATCCCGGACGTT
                *****
Smith3_419      GGTAATCTCTCTCAGGTAGTTGTAATGAAATCCAAGAACGACCAAGGTATCACTAACAAATGCAAAATGAATCTGCAGGACAACAAATGGTAACGATATCGGTTCATCGGTTTCCACCAG
Kink22_139      GGTAATCTCTCTCAGGTAGTTGTAATGAAATCCAAGAACGACCAAGGTATCACTAACAAATGCAAAATGAATCTGCAGGACAACAAATGGTAACGATATCGGTTCATCGGTTTCCACCAG
                *****
Smith3_419      TTCAACAAATATCGCTAAACTGGTTGCTTCCAACCTGGTACAATCGTCAGATCGAACGTTCCTCTCGCACTCTGGGTGCTCTTGGGAGTTATCCCGGTTGATGACGGTTGGGGTGAACGT
Kink22_139      TTCAACAAATATCGCTAAACTGGTTGCTTCCAACCTGGTACAATCGTCAGATCGAACGTTCCTCTCGCACTCTGGGTGCTCTTGGGAGTTATCCCGGTTGATGACGGTTGGGGTGAACGT
                *****
Smith3_419      CCGCTGTAA-----GAATTC--
Kink22_139      CCGCTGTAAACCCGGAAAGCTT
                *****
```

### Alignment 3

Smith SEQ ID NO:4 (hereinafter "Smith4\_419") was aligned with the amino acid sequence of SEQ ID NO:22 of Kink (U.S. Pat. No. 5,736,139; hereinafter "Kink22\_139"). Identical amino acids are marked by an asterix highlighted in yellow.

```

Smith4_419      M---STFTYIKNIINTSILNLRYESNHLIDLRYASKINIGSKVNFDPIDKNQIQLFNLESSKIEVILKNAIVNSMYENFSTSFWIRIPKYFNSISLNNEYTIINCMENNSGKWVSL
Kink22_139      MARLLSTFTYIKNIINTSILNLRYESNHLIDLRYASKINIGSKVNFDPIDKNQIQLFNLESSKIEVILKNAIVNSMYENFSTSFWIRIPKYFNSISLNNEYTIINCMENNSGKWVSL
                  *
Smith4_419      NYGEIIWTLQDTQEIQRVVFYKYSQMINISDYINRWIFVTITNNRLNNSKIYINGRLIDQKPIISNLGNIHASNNIMFKLDGCRDTHRYIWIKYFNLFDKELNEKEIKDLYDNQSNSGILK
Kink22_139      NYGEIIWTLQDTQEIQRVVFYKYSQMINISDYINRWIFVTITNNRLNNSKIYINGRLIDQKPIISNLGNIHASNNIMFKLDGCRDTHRYIWIKYFNLFDKELNEKEIKDLYDNQSNSGILK
                  *
Smith4_419      DFWGDYLYDKPYMYMLNLYDPNKYVDVNVVGIRGYMYLKGPRGSVMTTNIYLNSSLYRGTKFIIKKYASGNKDNIVRNNDRVYINVVVKNEYRLATNASQAGVEKILSALEIPDVGNLS
Kink22_139      DFWGDYLYDKPYMYMLNLYDPNKYVDVNVVGIRGYMYLKGPRGSVMTTNIYLNSSLYRGTKFIIKKYASGNKDNIVRNNDRVYINVVVKNEYRLATNASQAGVEKILSALEIPDVGNLS
                  *
Smith4_419      QVVVMKSKNDQGITNKCKMNLQDNNNGNDIGFIFGHQFNNAKLVASNWNRYQIERSSRTLGCSEWFI PVDDGWGERPL
Kink22_139      QVVVMKSKNDQGITNKCKMNLQDNNNGNDIGFIFGHQFNNAKLVASNWNRYQIERSSRTLGCSEWFI PVDDGWGERPL
                  *

```

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Smith et al.  
Serial No. : 09/611,419 Examiner : Portner, V.  
Filed : July 06, 2000 Group Art Unit : 1645  
For : RECOMBINANT VACCINE AGAINST BOTULINUM NEUROTOXIN

AMENDMENT AND SUBMISSION OF SUBSTITUTE  
SEQUENCE LISTING

I hereby certify that this paper is being deposited with the United States Postal  
Service as first class mail in an envelope addressed to: Assistant Commissioner for  
Patents, Washington, D.C. 20231

March 5, 2002 ✓  
Date of Deposit

Rochelle K. Seide  
Attorney Name

Rochelle K. Seide  
Signature

32,300  
PTO Registration No.

March 5, 2002  
Date of Signature

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Applicants submit this paper in response to the Office Communication dated  
September 7, 2001 that was issued in the above-identified application. Applicants also enclose  
herewith a Substitute Sequence Listing. Applicants request a five month extension of time and  
enclose the fee required pursuant to 37 C.F.R. §1.17(a)(5).

IN THE SPECIFICATION

Please **delete** the Sequence Listing presently of record and substitute, therefor, the attached Substitute Sequence Listing.

Please **amend** the paragraph beginning at page 12, line 7 and ending at page 12, line 14 with the following rewritten paragraph:

--Kozaki et al. (*in* "Antibodies against Botulism Neurotoxin", L.L. Simpson, ed., 1989, Academic Press, New York) suggested that a protective epitope might be present in the 50 kDa carboxyl terminus (HC) region of the protein. Thompson et al. (1990, *Eur. J. Biochem.* **189**:73-81) deduced the amino acid sequence for the serotype A botulinum toxin. DasGupta et al. (1990, *Biochemie*, **72**:661-664) identified the "nick" site for post-translational cleavage of the expressed toxin polypeptide, from which the sequence of the heavy chain can be deduced as SEQ ID NO:41. See also Krieglstein, et al., 1994, *J. Protein Chem.*, **13**:49-57.--

b Please **delete** the sequence paragraph beginning at page 12, line 15 and ending at page 12, line 31.

Please **amend** the paragraph beginning at page 13, line 1 and ending at page 13, line 6 with the following rewritten paragraph:

--Whelan et al. (*Appl. Environ. Microbiol.* **58**:2345-2354, 1992) have deduced the amino acid sequence for the serotype B botulinum toxin. Schmidt, et al. (1985, *Arch. Biochem. Biophys.*, **238**:544-548) provided N-terminal sequence information for the heavy chain resulting from post-translational cleavage of the expressed toxin polypeptide, and the sequence of the heavy chain can be deduced from this information as SEQ ID NO:42.--

Please **delete** the sequence paragraph beginning at page 13, line 8 and ending at page 13, line 24.

Please **amend** the paragraph beginning at page 36, line 17 and ending at page 36, line 17 with the following rewritten paragraph:

--The sequence of the C fragment of the A chain was deduced as SEQ ID NO:38.--

d Please **delete** the sequence paragraph beginning at page 36, line 18 and ending at page 36, line 26.

Please **amend** the paragraph beginning at page 36, line 32 and ending at page 36, line 32 with the following rewritten paragraph:

--The sequence for the synthetic gene is SEQ ID NO:37.--

e Please **delete** the sequence paragraph beginning at page 37, line 1 and ending at page 37, line 27.

Please **amend** the paragraph beginning at page 38, line 6 and ending at page 38, line 7 with the following rewritten paragraph:

--The C fragment for botulism toxin serotype B of Whelan was studied and the portion of the protein having the sequence of SEQ ID NO:40 was defined as the C fragment.--

f Please **delete** the sequence paragraph beginning at page 38, line 8 and ending at page 38, line 16.

Please **delete** the paragraph beginning at page 38, line 17 and ending at page 38, line 17.

Please **amend** the paragraph beginning at page 38, line 18 and ending at page 38, line 25 with the following rewritten paragraph:

--The synthetic gene for expression in *E. coli* was produced in the manner described for synthesis of the gene for the C fragment of the A strand, namely, using a large number of oligomers of approximately 60-65 bases corresponding to the sequences of the + and - strands with overlaps of 7 bases. The oligomers were allowed to anneal and were ligated to form subunits of 250-300 base pairs each. Each subunit had been designed to have restriction

sites at their termini which allowed them to be assembled in the right order to form the complete gene. The synthetic gene encoding the C fragment of the B toxin is SEQ ID NO:39.--

Please **delete** the sequence paragraph beginning at page 38, line 26 and ending at page 39, line 21.



REMARKS

Applicants submit this paper in response to the Office Communication dated September 7, 2001 that was issued in the above-identified application. Applicants also enclose herewith a Substitute Sequence Listing. Applicants request a five month extension of time and enclose the fee required pursuant to 37 C.F.R. §1.17(a)(5).

Claims 39-86 are pending.

Rewritten paragraphs appear in the preceding "IN THE SPECIFICATION" section. Attached hereto is a marked-up version of the changes made to the specification paragraphs by the instant amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE" and is included pursuant to 37 C.F.R. §1.121(c)(ii). Should any discrepancies be discovered, the version presented in the preceding "IN THE SPECIFICATION" section shall take precedence.

Applicants submit herewith a Substitute Sequence Listing in paper and computer readable form. I hereby state that the content of the paper and computer readable copies of the Substitute Sequence Listing submitted in accordance with 37 C.F.R. §1.821(c) and (e), are the same. I hereby state that the content of the paper and computer readable copies of the Substitute Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(g), herein does not include new matter.

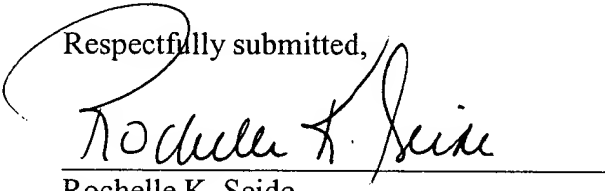
Applicants Substitute Sequence Listing corrects typographical errors in the sequences presented in the original application. Applicants enclose herewith five sequence alignments for the Examiner's review wherein corrections are highlighted. In each case, the

Examiner's attention is respectfully invited to the aligned sequences which provide support for the changes.

The Commissioner is hereby authorized to charge any fees due with this submission not otherwise enclosed to Deposit Account No. 02-4377. Please credit any overpayment of fees associated with this filing to the above-identified deposit account. A duplicate of this page is enclosed.

A copy of the Notice to Comply is enclosed.

Respectfully submitted,



Rochelle K. Seide  
PTO Reg. No. 32,300  
Attorney for Applicant

BAKER BOTTS, L.L.P.  
30 Rockefeller Plaza  
New York, NY 10112  
(212) 408-2626

Enclosures

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION**

This marked-up version was prepared with DeltaView (v2.5.163) software. In this section, added text is marked with double underlining. e.g. added text, and deleted text is marked by a single strikethrough, e.g. ~~deleted text~~.

The paragraph beginning at page 12, line 7 and ending at page 12, line 14 has been **amended** as follows:

Kozaki et al. (*in* "Antibodies against Botulism Neurotoxin", L.L. Simpson, ed., 1989, Academic Press, New York,) suggested that a protective epitope might be present in the 50 kDa carboxyl terminus (HC) region of the protein. Thompson et al. (1990, *Eur. J. Biochem.* **189**:73-81) deduced the amino acid sequence for the serotype A botulinum toxin. DasGupta, et al. (1990, *Biochemie*, **72**:661-664), identified the "nick" site for post-translational cleavage of the expressed toxin polypeptide, from which the sequence of the heavy chain can be deduced as follows (~~see~~SEQ ID NO:41. See also Krieglstein, et al., 1994, *J. Protein Chem.*, **13**:49-57):57.

The sequence paragraph beginning at page 12, line 15 and ending at page 12, line 31 has been **deleted**.

ALNDLCIKVNNWDLFFSPSEDNFTNDLNKGEEITSDTNIEAAEENISLDLIQQYYL  
TFNFDNEPENISIENLSSDHGQLELMPNTERFPNGKKYELDKYTMFHYLRAQEFEGHKS  
IALTNSVNEALLNPSRVYTFSSDYVKKVNKATEAAMFLGWVEQLVYDFTDETSEVSTT  
DKIADITHHPYIGPALNIGMLYKDDFVGALIFSGAVILLEFIPEIAIPVLGTFALVSYIANKV  
LTVQTIDNALS KRNEKWDEVYKYIVTNWLAKVNTQIDLRKKMKEALENQAEATKAH  
NYQYNQYTEEEKNNINFNIDDLSSKLNESINKAMININKFLNQCSVSILMNSMIPYGVK  
RLEDFDASLKDALLKYIRDNYGTLIGQVDRDKDKVNNTLSTDIPFQLSKYVDNQRLST  
FTEYIKNIINTSILNLRYESNHLIDLSRYASKINIGSKVNFDPIDKNQIQLFNLESSKIEVILK  
NAIVYNSMYENFSTSFWRIPKYFNSISLNNEYTIINC MENNSGWKVSLNYGEIHWTLQDT  
QEIQRVVFVKYSQMINISDYINRWIFVTITNNRLNNSKIYTINGRLIDQKPISNLGNIHASN  
NIMFKLDGCRDTHRYIWIKYFNLFDKELNEKEIKDLYDNQSN SGILKDFWGDYLYQYDKP  
YYMILLYDPNKYVDVNNVGIRGYMYLKGPRGSVMTTNIYLNSSLYRGTKFHKKASGN  
KDNIVRNNDRVYINVVVKNEYRLATNASQAGVEKILSALEIPDVGNLSQVVVMKSKN  
DQGITNKCKMNLQDNNGNDIGFIGFHQFNIAKLVASNWNROTERSSRTLGCSEWEIFP  
VDDGWGERPL

The paragraph beginning at page 13, line 1 and ending at page 13, line 6 has been  
**amended** as follows:

Whelan et al. (*Appl. Environ. Microbiol.* **58**:2345-2354, 1992) have deduced the  
amino acid sequence for the serotype B botulinum toxin. Schmidt, et al. (1985, *Arch. Biochem.*  
*Biophys.*, **238**:544-548); provided N-terminal sequence information for the heavy chain resulting

~~form~~from post-translational cleavage of the expressed toxin polypeptide, and the sequence of the heavy chain can be deduced from this information as followsSEQ ID NO:42.

The sequence paragraph beginning at page 13, line 8 and ending at page 13, line 24 has been deleted.

APGICIDVDNEDLFFIADKNSFSDDLKNERIEYNTQSNIYIENDFPINELILD TD LIS  
KIELPSENTESLTDFNVDPVYVEKQPAIKKIFTDENTIFQYLYSQTFPLDIRDISLTSSFDDA  
LLFSNKVYSFFSMDYIKTANKVVEAGLFAGWVKQIVNDFVIEANKSNTMDKIADISLIVP  
YIGLALNVGNETAKGNFENAFELIAGASILLEFIPELLIPVVGAFLLSYIDNKNKHKITDN  
ALTKRNEKWSDMYGLIVAQWLSTVNTQFYTIKEGMYKALNYQAQALEEIKYRYNIYS  
EKEKSNINIDFNDINSKLNEGINQAIDNINNFINGCSVSYLMKKMPLAVEKLLDFDNTLK  
KNLLNYIDENKLYLIGSAEYEKSKVNKYLKTIMPFDLSTYTNDTILIEMFNKYNSEILNNH  
LNLRYKDNNLIDLSGYGAKVEVYDGVELNDKNQFKLTSSANSKIRTTQNQNIHFNSVFL  
DFSVSFWIRIPKYKNDGIQNYIHNEYTHNCMKNNSGWKISIRGRIIWTLIDINGKTKSVFF  
EYNIREDISEYINRWFFVTITNNLNNAKIYINGKLESNTDIKDIREVIANGEIIFKLDGDIDR  
TQFIWMKYFSIFNTELSQSNIERYKIQSYSEYLKDFWGNPLMYNKEYYMFNAGNKNSY  
TIKLLKDSPVGEILTRSKYNQNSKYINYRDLYIGEKFHRRKSNSQSINDDIVRKEDYIYLD  
FFNLNQEWRVYTYKYFKKEEELFLAPISDSDEFYNTIQIKEYDEQPTYSCQLLFKKDEES  
TDEIGLIGHRFYESGIVFEEVKDVFCISDWYLEVKKRKPYNLKLGCNWQFIPKDEGWTE

The paragraph beginning at page 36, line 17 and ending at page 36, line 17 has been **amended** as follows:

The sequence of the C ~~fragment~~fragment of the A chain was deduced as SEQ ID NO:38.

The sequence paragraph beginning at page 36, line 18 and ending at page 36, line 26 has been **deleted**.

RYESNHLIDLSRYASKINIGSKVNFDPIDKNQIQLFNLESSKIEVILKNAIVYNSMY  
ENFSTSFWIRIPKYFNSISLNNEYTHNCMENNSGWKVS LNYGEIHWTLQDTQEIQRVVF  
KYSQMINISDYINRWIFVTITNNRLNNSKIYINGRLIDQKPISNLGNIHASNNIMFKLDGCR  
DTHRYIWIIFYFNLFDKELNEKEIKDLYDNQSN SGILKDFWGDYLYDKPYYMLNLYDP  
NKYVDVNNVGI RGYMYLK GPRGSVMTTNIYLNSSLYRGTKFIKKYASGNKDNIVRNN  
DRVYINVVVKNKEYRLATNASQAGVEKILSALEIPDVGNLSQVVVMKSKNDQGITNKC  
KMN LQDNNNGNDIGFIGFHQFN NIAKLVASNWYNRQIERSSRTLGC SWEFIPVDDGWGE  
RPL

The paragraph beginning at page 36, line 32 and ending at page 36, line 32 has been **amended** as follows:

The sequence for the synthetic gene is ~~found below:~~SEQ ID NO:37.

The sequence paragraph beginning at page 37, line 1 and ending at page 37, line 27 has been **deleted**.

CTCGAGCCATGGCTCGTCTGCTGTCTACCTTCACTGAATACATCAAGAACATC  
ATCAATACCTCCATCCTGAACCTGCGCTACGAATCCAATCACCTGATCGACCTGTCT  
CGCTACGCTTCCAAAATCAACATCGGTTCTAAACTTAACTTCGATCCGATCGACAAG  
AATCAGATCCAGCTGTTCAATCTGGAATCTTCCAAAATCGAAGTTATCCTGAAGAAT  
GCTATCGTATACAACCTCTATGTACGAAAACCTTCTCCACCTCCTTCTGGATCCGTATCC  
CAAATACTTCAACTCCATCTCTCTGAACAATGAATACACCATCATCAACTGCATGGA  
AAACAATTCTGGTTGGAAAGTATCTCTGAACTACGGTGAAATCATCTGGACTCTGCA  
GGACACTCAGGAAATCAAACAGCGTGTTGTATTCAAATACTCTCAGATGATCAACA  
TCTCTGACTACATCAATCGCTGGATCTTCGTTACCATCACCAACAATCGTCTGAATA  
ACTCCAAAATCTACATCAACGCCGTCTGATCGACCAGAAACCGATCTCCAATCTGG  
GTAACATCCACGTTCTAATAACATCATGTTCAAACCTGGACGGTTGTCGTGACACTCA  
CCGCTACATCTGGATCAAATACTTCAATCTGTTGACAAAGAAGTGAACGAAAAAG  
AAATCAAAGACCTGTACGACAACCAGTCCAATTCTGGTATCCTGAAAGACTTCTGG  
GGTGACTACCTGCAGTACGACAAACCGTACTACATGCTGAATCTGTACGATCCGAA  
CAAATACGTTGACGTCAACAATGTAGGTATCCGCGGTTACATGTACCTGAAAGGTC  
CGCGTGGTTCTGTTATGACTACCAACATCTACCTGAACTCTTCCCTGTACCGTGGTA  
CCAAATTCATCATCAAGAAATACGCGTCTGGTAACAAGGACAATATDCGCAACAAT  
GATCGTGTATACATCAATGTTGTAGTTAAGAACAAGAATACCGTCTGGCTACCAAT  
GCTTCTCAGGCTGGTGTAGAAAAGATCTTGTCTGCTCTGGAAATCCCGGACGTTGGT  
AATCTGTCTCAGGTAGTTGTAATGAAATCCAAGAACGACCAGGGTATCACTAACAA

ATGCAAAATGAATCTGCAGGACAACAATGGTAACGATATCGGTTTCATCGGTTTCC  
ACCAGTTCAACAATATCGCTAAACTGGTTGCTTCCAACCTGGTACAATCGTCAGATCG  
AACGTTCTCTCGCACTCTGGGTTGCTCTTGGGAGTTCATCCCGGTTGATGACGGTT  
GGGGTGAACGTCCGCTGTAACCCGGGAAAGCTT

The paragraph beginning at page 38, line 6 and ending at page 38, line 7 has been **amended** as follows:

The C fragment for botulism toxin serotype B of Whelan was studied and the portion of the protein having the sequence of SEQ ID NO:40 was defined as the C fragment.

The sequence paragraph beginning at page 38, line 8 and ending at page 38, line 16 has been **deleted**.

FNKYNSEILNNIILNLRKDNNDLSGYGAKVEVYDGVELNDKNQFKLTSSANS  
KIRVTQNQNIIFNSVFLDFSVSFWRIPKYKNDGIQNYIHNEYTHNCMKNNSGWKISIRGN  
RITWTLIDINGKTKSVFFEYNIREDISEYINRWFFVTITNNLNNAKIYINGKLESNTDIKDIR  
EVIANGEIIFKLDGDIIDRTQFIWMKYFSIFNTELSQSNIERYKIQSYSEYKDFWGNPLM  
YNKEYYMFNAGNKNSYIKLKKDSPVGEILTRSKYNQNSKYINYRDLYIGEKFHRRKSNS  
QSINDDIVRKEDYIYLDFF-  
NLNQEQRVYTYKKFKKEEEKLFLAPISDSDEFYNTIQIKEYDEQPTY



~~SCQLLFKKDEESTDEIGLIGHRFYESGIVFEEYKDYFCISKWYLKEVKRKPYNLKLCN~~  
~~WQFIPKDEGWTE~~

The paragraph beginning at page 38, line 17 and ending at page 38, line 17 has been **deleted**.

~~was defined as the C fragment.~~

The paragraph beginning at page 38, line 18 and ending at page 38, line 25 has been **amended** as follows:

The synthetic gene for expression in *E. coli* was produced in the manner described for synthesis of the gene for the C fragment of the A strand, namely, using a large number of oligomers of approximately 60-65 bases corresponding to the sequences of the  $\underline{+}$  and  $\underline{-}$  strands with overlaps of 7 bases. The oligomers were allowed to anneal and were ligated to form subunits of 250-300 base pairs each. Each subunit had been designed to have restriction sites at their termini which allowed them to be assembled in the right order to form the complete gene. ~~the~~The synthetic gene for encoding the eC fragment of the B toxin ~~was as follows~~is SEQ ID NO:39.

The sequence paragraph beginning at page 38, line 26 and ending at page 39, line 21 has been **deleted**.

ATGGCTTTCAACAAATACAATTCCGAAATCCTGAACAATATCATCCTGAACC  
TGCGTTACAAAGACAACAATCTGATCGATCTGTCTGGTTACGGTGCTAAAGTTGAAG  
TATACGACGGTGTTGAACTGAATGACAAGAACCAGTTCAAACCTGACCTCTTCCGCTA  
ACTCTAAGATCCGTGTTACTCAGAATCAGAACATCATCTTCAACTCCGTATTCCCTGG  
ACTTCTCTGTTTCCTTCTGGATCCGTATCCCGAAATACAAGAACGACGGTATCCAGA  
ATTACATCCACAATGAATACACCATCATCAACTGCATGAAGAATAACTCTGGTTGG  
AAGATCTCCATCCGCGGTAACCGTATCATCTGGACTCTGATCGATATCAACGGTAAG  
ACCAAATCTGTATTCTTCGAATACAACATCCGTGAAGACATCTCTGAATACATCAAT  
CGCTGGTTCTTCGTTACCATCACCAATAACCTGAACAATGCTAAAATCTACATCAAC  
GGTAAACTGGAATCTAATACCGACATCAAAGACATCCGTGAAGTTATCGCTAACGG  
TGAAATCATCTTCAAACCTGGACGGTGACATCGATCGTACCCAGTTCATCTGGATGAA  
ATACTTCTCCATCTTCAACACCGAACTGTCTCAGTCCAATATCGAAGAACGGTACAA  
GATCCAGTCTTACTCCGAATACCTGAAAGACTTCTGGGGTAATCCGCTGATGTACAA  
CAAAGAATACTATATGTTCAATGCTGGTAACAAGAAGTCTTACATCAAACCTGAAGA  
AAGACTCTCCGGTTGGTGAATCCTGACTCGTTCCAAATACAACCAGAACTCTAAATA  
CATCAACTACCGCGACCTGTACATCGGTGAAAAGTTCATCATCCGTCCGAAATCTAA  
CTCTCAGTCCATCAATGAGACATCGTACGTAAAGAAGACTACATCTACCTGGACTTC  
TTCAACCTGAATCAGAATGGCGTGTATACACCTACAAGTACTTCAAGAAAGAAGAA  
GAAAAGCTTTTCCTGGCTCCGATCTCTGATTCCGACGAACCTCTACAACACCATCCAG  
ATCAAAGAATACGACGAACAGCCGACCTACTCTTGCCAGCTGCTGTTCAAGAAAGA

TGAAGAATCTACTGACGAAATCGGTCTGATCGGTATCCACCGTTTCTACGAATCTGG  
TATCGTATTCGAAGAATACAAAGACTCTTCTGCATCTCCAAATGGTACCTGAAGGAA  
GTTAAACGCAAACCGTACAACCTGAAACTGGGTTGCAATTGGCAGTTCATCCCGAA  
AGACGAAGGTTGGACCGAATAGTAACCTCTAGAGTCGAGGCCTGCAG

### IN THE SEQUENCE LISTING

The following alignments show the changes made to the indicated sequences and the support for these changes based on other sequences in the application. In this section, a summary of changes appears just before each alignment and changes are highlighted in the alignments. (SI# = SEQ ID NO; Ac# M81186 = Genbank accession number M81186, a copy of which is attached.)

### Alignment 1

SEQ ID NO:41 (appearing on page 12 in the specification as filed) has been amended as follows:

- At position 717 of paragraph 1.8, Y has been inserted.
- At position 822 of paragraph 1.10,  $O \rightarrow Q$ .

Paragraph 1.1	15	16	30	31	45	46	60	61	75	76
As filed	ALNDLCIKVNNWDLF	FSPSEDNFTNDLNG	EEITSDTNIEAAEEN	ISLDLIQQYYLTFNF	DNEPENISIEENLSSD	IIGQLELMPNIERFP				90
Amended	ALNDLCIKVNNWDLF	FSPSEDNFTNDLNG	EEITSDTNIEAAEEN	ISLDLIQQYYLTFNF	DNEPENISIEENLSSD	IIGQLELMPNIERFP				90
p.36 SI#38	-----	-----	-----	-----	-----	-----				0
Fig.3 SI#6	-----	-----	-----	-----	-----	-----				0
Fig.2 SI#4	-----	-----	-----	-----	-----	-----				0
Fig.1 SI#2	-----	-----	-----	-----	-----	-----				0

Paragraph 1.2

91	105	106	120	121	135	136	150	151	165	166	180
As filed	NGKKYELDKYTMFHY	LRAQEFHGKSRIAL	TNSVNEALINPSRVY	TFSSDYVKKVKNKAT	EAAMFLGWVEQLVYD	FTDETSEVSTTDKIA	180				
Amended	NGKKYELDKYTMFHY	LRAQEFHGKSRIAL	TNSVNEALINPSRVY	TFSSDYVKKVKNKAT	EAAMFLGWVEQLVYD	FTDETSEVSTTDKIA	180				
P.36 SI#38	-----	-----	-----	-----	-----	-----	0				
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	0				
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	0				
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	0				

Paragraph 1.3

181	195	196	210	211	225	226	240	241	255	256	270
As filed	DITIIIPYIGPALNI	GMLYKDDFVGALIFS	GAVILLEFIPEIAIP	VLGTFALVSYIANKV	LTVOITIDNALS KRNE	KWDEVYKYIIVTNWLA	270				
Amended	DITIIIPYIGPALNI	GMLYKDDFVGALIFS	GAVILLEFIPEIAIP	VLGTFALVSYIANKV	LTVOITIDNALS KRNE	KWDEVYKYIIVTNWLA	270				
P.36 SI#38	-----	-----	-----	-----	-----	-----	0				
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	0				
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	0				
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	0				

Paragraph 1.4

271	285	286	300	301	315	316	330	331	345	346	360
As filed	KVNTQIDILIRKKMKE	ALENQAEATKAIINY	QYNQYTEEEKNNINF	NIDDLSSKLNESINK	AMININKFLNQCSVS	YLMNSMIPYGVKRLE	360				
Amended	KVNTQIDILIRKKMKE	ALENQAEATKAIINY	QYNQYTEEEKNNINF	NIDDLSSKLNESINK	AMININKFLNQCSVS	YLMNSMIPYGVKRLE	360				
P.36 SI#38	-----	-----	-----	-----	-----	-----	0				
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	0				
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	0				
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	0				

Paragraph 1.5

361	375	376	390	391	405	406	420	421	435	436	450
As filed	DFDASLKDALLKYIR	DNYGTLIGQVDRLLKD	KVNNTLSTDIPFQLS	KYVDNQRLSTFTEY	IKNIINTSILNRYE	SNHLIDLSRYASKIN	450				
Amended	DFDASLKDALLKYIR	DNYGTLIGQVDRLLKD	KVNNTLSTDIPFQLS	KYVDNQRLSTFTEY	IKNIINTSILNRYE	SNHLIDLSRYASKIN	450				
P.36 SI#38	-----	-----	-----	-----	-----	-----	18				
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	38				
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	37				
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	40				

Paragraph 1.6  
451 As filed IGSKVNFDPIDKNQI QLFNLESSKIEVILK NAIVNSMYENFSTS FWIRIPKYPNSISLN NEYTIINCMMENNSGW KVS LNYGEI IWT LQD 540  
Amended IGSKVNFDPIDKNQI QLFNLESSKIEVILK NAIVNSMYENFSTS FWIRIPKYPNSISLN NEYTIINCMMENNSGW KVS LNYGEI IWT LQD 540  
P.36 SI#38 IGSKVNFDPIDKNQI QLFNLESSKIEVILK NAIVNSMYENFSTS FWIRIPKYPNSISLN NEYTIINCMMENNSGW KVS LNYGEI IWT LQD 108  
Fig.3 SI#6 IGSKVNFDPIDKNQI QLFNLESSKIEVILK NAIVNSMYENFSTS FWIRIPKYPNSISLN NEYTIINCMMENNSGW KVS LNYGEI IWT LQD 128  
Fig.2 SI#4 IGSKVNFDPIDKNQI QLFNLESSKIEVILK NAIVNSMYENFSTS FWIRIPKYPNSISLN NEYTIINCMMENNSGW KVS LNYGEI IWT LQD 127  
Fig.1 SI#2 IGSKVNFDPIDKNQI QLFNLESSKIEVILK NAIVNSMYENFSTS FWIRIPKYPNSISLN NEYTIINCMMENNSGW KVS LNYGEI IWT LQD 130

Paragraph 1.7  
541 As filed TQEIQRVWFKYSQM INISDYINRWIFVTI TNNRLNNSKIYTING RLIDQKPI SNLGNH ASNNIMFKLDGCRDT HRYIWI KYFN LFDKE 630  
Amended TQEIQRVWFKYSQM INISDYINRWIFVTI TNNRLNNSKIYTING RLIDQKPI SNLGNH ASNNIMFKLDGCRDT HRYIWI KYFN LFDKE 630  
P.36 SI#38 TQEIQRVWFKYSQM INISDYINRWIFVTI TNNRLNNSKIYIN-G RLIDQKPI SNLGNH ASNNIMFKLDGCRDT HRYIWI KYFN LFDKE 197  
Fig.3 SI#6 TQEIQRVWFKYSQM INISDYINRWIFVTI TNNRLNNSKIYIN-G RLIDQKPI SNLGNH ASNNIMFKLDGCRDT HRYIWI KYFN LFDKE 217  
Fig.2 SI#4 TQEIQRVWFKYSQM INISDYINRWIFVTI TNNRLNNSKIYIN-G RLIDQKPI SNLGNH ASNNIMFKLDGCRDT HRYIWI KYFN LFDKE 216  
Fig.1 SI#2 TQEIQRVWFKYSQM INISDYINRWIFVTI TNNRLNNSKIYIN-G RLIDQKPI SNLGNH ASNNIMFKLDGCRDT HRYIWI KYFN LFDKE 219

Paragraph 1.8  
631 As filed LNEKEIKDLYDNQSN SGILKDFWGDYLYD KPYMILLYDPNKYV DVNNVGIRGYMYLKG PRGSVMTTNIYLNSS LYRGTKFIIKKYASG 719  
Amended LNEKEIKDLYDNQSN SGILKDFWGDYLYD KPYMILLYDPNKYV DVNNVGIRGYMYLKG PRGSVMTTNIYLNSS LYRGTKFIIKKYASG 719  
P.36 SI#38 LNEKEIKDLYDNQSN SGILKDFWGDYLYD KPYMILLYDPNKYV DVNNVGIRGYMYLKG PRGSVMTTNIYLNSS LYRGTKFIIKKYASG 287  
Fig.3 SI#6 LNEKEIKDLYDNQSN SGILKDFWGDYLYD KPYMILLYDPNKYV DVNNVGIRGYMYLKG PRGSVMTTNIYLNSS LYRGTKFIIKKYASG 307  
Fig.2 SI#4 LNEKEIKDLYDNQSN SGILKDFWGDYLYD KPYMILLYDPNKYV DVNNVGIRGYMYLKG PRGSVMTTNIYLNSS LYRGTKFIIKKYASG 306  
Fig.1 SI#2 LNEKEIKDLYDNQSN SGILKDFWGDYLYD KPYMILLYDPNKYV DVNNVGIRGYMYLKG PRGSVMTTNIYLNSS LYRGTKFIIKKYASG 309

Paragraph 1.9  
721 As filed NKDNIVRNNDRVYN VVVKNEYRLATNAS QAGVEKILSALEIPD VGNLSQVVMKSKND QGITNKCKMNLQDNN GNDIGFIGFHQFNFI 809  
Amended NKDNIVRNNDRVYN VVVKNEYRLATNAS QAGVEKILSALEIPD VGNLSQVVMKSKND QGITNKCKMNLQDNN GNDIGFIGFHQFNFI 809  
P.36 SI#38 NKDNIVRNNDRVYN VVVKNEYRLATNAS QAGVEKILSALEIPD VGNLSQVVMKSKND QGITNKCKMNLQDNN GNDIGFIGFHQFNFI 377  
Fig.3 SI#6 NKDNIVRNNDRVYN VVVKNEYRLATNAS QAGVEKILSALEIPD VGNLSQVVMKSKND QGITNKCKMNLQDNN GNDIGFIGFHQFNFI 397  
Fig.2 SI#4 NKDNIVRNNDRVYN VVVKNEYRLATNAS QAGVEKILSALEIPD VGNLSQVVMKSKND QGITNKCKMNLQDNN GNDIGFIGFHQFNFI 396  
Fig.1 SI#2 NKDNIVRNNDRVYN VVVKNEYRLATNAS QAGVEKILSALEIPD VGNLSQVVMKSKND QGITNKCKMNLQDNN GNDIGFIGFHQFNFI 399

Paragraph 1.10	811	825	826	840	841	855	856	870	871	885	886	900
As filed	AKLVASNNWYNRQIER	SSRTLGC	SWEFIPVD	DWGERPL		846						
Amended	AKLVASNNWYNRQIER	SSRTLGC	SWEFIPVD	DWGERPL		847						
P.36 SI#38	AKLVASNNWYNRQIER	SSRTLGC	SWEFIPVD	DWGERPL		415						
Fig.3 SI#6	AKLVASNNWYNRQIER	SSRTLGC	SWEFIPVD	DWGERPL		435						
Fig.2 SI#4	AKLVASNNWYNRQIER	SSRTLGC	SWEFIPVD	DWGERPL		434						
Fig.1 SI#2	AKLVASNNWYNRQIER	SSRTLGC	SWEFIPVD	DWGERPL		437						

## Alignment 2

SEQ ID NO:42 (appearing on page 13 in the specification as filed) has been amended as follows:

- At position 911 of paragraph 2.11, T→V.
- At position 969 of paragraph 2.11, N has been inserted.
- At position 1110 of paragraph 2.13, T has been deleted.
- At position 1193 of paragraph 2.14, K has been inserted.
- At position 1254 of paragraph 2.14, V→Y.
- At position 1257 of paragraph 2.14, V→Y.
- At position 1262 of paragraph 2.15, D→K.
- At position 1269 of paragraph 2.15, K has been inserted.

Paragraph 2.1

NY02:373755.1

1 15 16 30 31 45 46 60 61 75 76 90  
As filed -----  
Amended -----  
Fig 4 SI#8 -----  
Ac# M81186 MPVTINNFVNDPID NNNIIMMEPPFARGT GRYYKAFKITDRIWI IPERYTFGYKPEDFN KSSGIFNRDVCYYD PDYLNTNDKKNIFLQ 0  
0  
0  
90

Paragraph 2.2  
91 105 106 120 121 135 136 150 151 165 166 180  
As filed -----  
Amended -----  
Fig 4 SI#8 -----  
Ac# M81186 TWIKLFNRIKSKPLG EKLEMIINGIPYLG DRRVPLEEFNTNIAS VTVNKLISNPGEVER KKGIFANLIIFGPGP VLNENETIDIGIQNH 0  
0  
0  
180

Paragraph 2.3  
181 195 196 210 211 225 226 240 241 255 256 270  
As filed -----  
Amended -----  
Fig 4 SI#8 -----  
Ac# M81186 FASREGFGIMQMKF CPEYVSFVNNVQENK GASIFNRRGYFSDPA LILMHელიHVLHGLY GIKVDDLPIVPNEKK FFMQSTDAIQAEELY 0  
0  
0  
270

Paragraph 2.4  
271 285 286 300 301 315 316 330 331 345 346 360  
As filed -----  
Amended -----  
Fig 4 SI#8 -----  
Ac# M81186 TFGGQDPSIITPSTD KSIYDKVLQNFVRGIV DRLNKVLVCISDPNI NINIYKNKFKDKYKF VEDSEGKYSIDVESF DKLYKSLMFGFTETN 0  
0  
0  
360

Paragraph 2.5  
361 375 376 390 391 405 406 420 421 435 436 450  
As filed -----  
Amended -----  
Fig 4 SI#8 -----  
Ac# M81186 IAENYKIKTRASYFS DSLPPVKIKNLLDNE IYTIIEEGFNISDKDM EKEYRGONKAINKQA YEEISKEHLAVYKIQ MCKSVKAPGICIDVD 9  
9  
0  
450



Paragraph 2.6									
451	465	466	480	481	495	496	510	511	525 526 540
As filed	NEDLFFIADKNSFSD	DLSKNERIEYNTQSN	YIENDFPINELI	DLT	DLISKIELPSENTES	LTDFNVDPVVEKQP	AIKKIFTDENTIFQY	99	
Amended	NEDLFFIADKNSFSD	DLSKNERIEYNTQSN	YIENDFPINELI	DLT	DLISKIELPSENTES	LTDFNVDPVVEKQP	AIKKIFTDENTIFQY	99	
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	0	
Ac# M81186	NEDLFFIADKNSFSD	DLSKNERIEYNTQSN	YIENDFPINELI	DLT	DLISKIELPSENTES	LTDFNVDPVVEKQP	AIKKIFTDENTIFQY	540	
Paragraph 2.7									
541	555	556	570	571	585	586	600	601	615 616 630
As filed	LYSQTFPLDIRDISL	TSSFDDALLFSNKVY	SFFSMDYIKTANKV	EAGLFAGWVKQIVND	FVIEANKSNTMDKIA	DISLIVPYIGLALNV	189		
Amended	LYSQTFPLDIRDISL	TSSFDDALLFSNKVY	SFFSMDYIKTANKV	EAGLFAGWVKQIVND	FVIEANKSNTMDKIA	DISLIVPYIGLALNV	189		
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	0	
Ac# M81186	LYSQTFPLDIRDISL	TSSFDDALLFSNKVY	SFFSMDYIKTANKV	EAGLFAGWVKQIVND	FVIEANKSNTMDKIA	DISLIVPYIGLALNV	630		
Paragraph 2.8									
631	645	646	660	661	675	676	690	691	705 706 720
As filed	GNETAKGNFENAFEI	AGASILLEFIPELLI	PVVGAFLLSEYIDNK	NKIIKTIDNALTKRN	EKWSMDYGLIVAQWL	STVNTQFYTIKEGMY	279		
Amended	GNETAKGNFENAFEI	AGASILLEFIPELLI	PVVGAFLLSEYIDNK	NKIIKTIDNALTKRN	EKWSMDYGLIVAQWL	STVNTQFYTIKEGMY	279		
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	0	
Ac# M81186	GNETAKGNFENAFEI	AGASILLEFIPELLI	PVVGAFLLSEYIDNK	NKIIKTIDNALTKRN	EKWSMDYGLIVAQWL	STVNTQFYTIKEGMY	720		
Paragraph 2.9									
721	735	736	750	751	765	766	780	781	795 796 810
As filed	KALNYQAQALEEIIK	YRYNIYSEKEKSIN	IDFNDINSKLNEN	QAIDNINNFINCSV	SYLMKKMIPLAVEKL	LDFDNTLKKNLLNYI	369		
Amended	KALNYQAQALEEIIK	YRYNIYSEKEKSIN	IDFNDINSKLNEN	QAIDNINNFINCSV	SYLMKKMIPLAVEKL	LDFDNTLKKNLLNYI	369		
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	0	
Ac# M81186	KALNYQAQALEEIIK	YRYNIYSEKEKSIN	IDFNDINSKLNEN	QAIDNINNFINCSV	SYLMKKMIPLAVEKL	LDFDNTLKKNLLNYI	810		
Paragraph 2.10									
811	825	826	840	841	855	856	870	871	885 886 900
As filed	DENKLYLIGSAEYK	SKVNKYLKTIMPFDL	SIYTNDTILIEFMNK	YNSEILNIIILNRY	KONNLIDLSGYGAKV	EVYDGVELNDKNQFK	459		
Amended	DENKLYLIGSAEYK	SKVNKYLKTIMPFDL	SIYTNDTILIEFMNK	YNSEILNIIILNRY	KONNLIDLSGYGAKV	EVYDGVELNDKNQFK	459		
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	49	
Ac# M81186	DENKLYLIGSAEYK	SKVNKYLKTIMPFDL	SIYTNDTILIEFMNK	YNSEILNIIILNRY	KONNLIDLSGYGAKV	EVYDGVELNDKNQFK	900		

Paragraph 2.11

901 915 916 930 931 945 946 960 961 975 976 990  
As filed LTSSANSKIRVTQNO NIIFNSVFLDFSVSF WIRIPKYKNDGIQNY IHNEYTIINCMKNN GWKISIRGNRIIWTL IDINGKTKSVFFEYN 548  
Amended LTSSANSKIRVTQNO NIIFNSVFLDFSVSF WIRIPKYKNDGIQNY IHNEYTIINCMKNN GWKISIRGNRIIWTL IDINGKTKSVFFEYN 549  
Fig 4 SI#8 LTSSANSKIRVTQNO NIIFNSVFLDFSVSF WIRIPKYKNDGIQNY IHNEYTIINCMKNN GWKISIRGNRIIWTL IDINGKTKSVFFEYN 139  
Ac# M81186 LTSSANSKIRVTQNO NIIFNSVFLDFSVSF WIRIPKYKNDGIQNY IHNEYTIINCMKNN GWKISIRGNRIIWTL IDINGKTKSVFFEYN 990

Paragraph 2.12

991 1005 1006 1020 1021 1035 1036 1050 1051 1065 1066 1080  
As filed IREDISEYINRWFFV TITNNLNNAKIYING KLESNTDIKDIREVI ANGEIIFKLDGDIR TQFIWMKYPSIFNTE LSQSNIEERYKIOSY 638  
Amended IREDISEYINRWFFV TITNNLNNAKIYING KLESNTDIKDIREVI ANGEIIFKLDGDIR TQFIWMKYPSIFNTE LSQSNIEERYKIOSY 639  
Fig 4 SI#8 IREDISEYINRWFFV TITNNLNNAKIYING KLESNTDIKDIREVI ANGEIIFKLDGDIR TQFIWMKYPSIFNTE LSQSNIEERYKIOSY 229  
Ac# M81186 IREDISEYINRWFFV TITNNLNNAKIYING KLESNTDIKDIREVI ANGEIIFKLDGDIR TQFIWMKYPSIFNTE LSQSNIEERYKIOSY 1080

Paragraph 2.13

1081 1095 1096 1110 1111 1125 1126 1140 1141 1155 1156 1170  
As filed SEYLKDFWGNPLMYN KEYYMFNAGNKNSY IKLKSDSPVGEILTR SKYNQNSKYINYRDL YIGEKFIIRKSN SQ SINDDIVRKEDYIYL 728  
Amended SEYLKDFWGNPLMYN KEYYMFNAGNKNSY IKLKSDSPVGEILTR SKYNQNSKYINYRDL YIGEKFIIRKSN SQ SINDDIVRKEDYIYL 728  
Fig 4 SI#8 SEYLKDFWGNPLMYN KEYYMFNAGNKNSY IKLKSDSPVGEILTR SKYNQNSKYINYRDL YIGEKFIIRKSN SQ SINDDIVRKEDYIYL 318  
Ac# M81186 SEYLKDFWGNPLMYN KEYYMFNAGNKNSY IKLKSDSPVGEILTR SKYNQNSKYINYRDL YIGEKFIIRKSN SQ SINDDIVRKEDYIYL 1169

Paragraph 2.14

1171 1185 1186 1200 1201 1215 1216 1230 1231 1245 1246 1260  
As filed DFFNLNQEWRYTYK YFKKEEELFLAPIS DSDEFYNTIQIKEYD EQPTYSQLLFKKDE ESTDEIGLIGIHRFY ESGIVFEEYKD YFCI 817  
Amended DFFNLNQEWRYTYK YFKKEEELFLAPIS DSDEFYNTIQIKEYD EQPTYSQLLFKKDE ESTDEIGLIGIHRFY ESGIVFEEYKD YFCI 818  
Fig 4 SI#8 DFFNLNQEWRYTYK YFKKEEELFLAPIS DSDEFYNTIQIKEYD EQPTYSQLLFKKDE ESTDEIGLIGIHRFY ESGIVFEEYKD YFCI 408  
Ac# M81186 DFFNLNQEWRYTYK YFKKEEELFLAPIS DSDEFYNTIQIKEYD EQPTYSQLLFKKDE ESTDEIGLIGIHRFY ESGIVFEEYKD YFCI 1259

Paragraph 2.15

1261 1275 1276 1290 1291 1305 1306 1320 1321 1335 1336 1350  
As filed SKWYLEVKEVRKPPYNL KLGCNWQFIPKDEGW TE 848  
Amended SKWYLEVKEVRKPPYNL KLGCNWQFIPKDEGW TE 850  
Fig 4 SI#8 SKWYLEVKEVRKPPYNL KLGCNWQFIPKDEGW TE 440  
Ac# M81186 SKWYLEVKEVRKPPYNL KLGCNWQFIPKDEGW TE 1291

### Alignment 3

SEQ ID NO:37 (appearing on page 37 in the specification as filed) has been amended as follows:

- At position 147 of paragraph 3.2, C→G.
- At position 287 of paragraph 3.4, G is inserted.
- At position 535 of paragraph 3.6, G is inserted.
- At position 583 of paragraph 3.7, C is inserted.
- At position 956 of paragraph 3.11, D→C.
- At positions 957-959 of paragraph 3.11, GTT is

Paragraph 3.1

1                   15 16                   30 31                   45 46                   60 61                   75 76                   90

As filed   ---CTCGAGCCATGG   CTCGTCTGCTGTCTA   CCTTCACCTGAATACA   TCAAGAACATCATCA   ATACCTCCATCCCTGA   ACCTGCGGTACGAAT   87

Amended   ---CTCGAGCCATGG   CTCGTCTGCTGTCTA   CCTTCACCTGAATACA   TCAAGAACATCATCA   ATACCTCCATCCCTGA   ACCTGCGGTACGAAT   87

Fig.1 SI#1   GAATTCGAAACGATG   CGT--CTGCTGTCTA   CCTTCACCTGAATACA   TCAAGAACATCATCA   ATACCTCCATCCCTGA   ACCTGCGGTACGAAT   88

Fig.3 SI#5   GAATTCGAAACGATG   G-----CCTCTA   CCTTCACCTGAATACA   TCAAGAACATCATCA   ATACCTCCATCCCTGA   ACCTGCGGTACGAAT   82

Fig.2 SI#3   GAATTCGAAACGATG   T-----CTA   CCTTCACCTGAATACA   TCAAGAACATCATCA   ATACCTCCATCCCTGA   ACCTGCGGTACGAAT   79

Paragraph 3.2

91                   105 106                   120 121                   135 136                   150 151                   165 166                   180

As filed   CCAATCACCTGATCG   ACCTGTCTCGTACG   CTTCCAAAATCAACA   TCGGTCTTAAAGTTA   ACTTCGATCCGATCG   ACAAGAATCAGATCC   177

Amended   CCAATCACCTGATCG   ACCTGTCTCGTACG   CTTCCAAAATCAACA   TCGGTCTTAAAGTTA   ACTTCGATCCGATCG   ACAAGAATCAGATCC   177

Fig.1 SI#1   CCAATCACCTGATCG   ACCTGTCTCGTACG   CTTCCAAAATCAACA   TCGGTCTTAAAGTTA   ACTTCGATCCGATCG   ACAAGAATCAGATCC   178

Fig.3 SI#5   CCAATCACCTGATCG   ACCTGTCTCGTACG   CTTCCAAAATCAACA   TCGGTCTTAAAGTTA   ACTTCGATCCGATCG   ACAAGAATCAGATCC   172

Fig.2 SI#3   CCAATCACCTGATCG   ACCTGTCTCGTACG   CTTCCAAAATCAACA   TCGGTCTTAAAGTTA   ACTTCGATCCGATCG   ACAAGAATCAGATCC   169

Paragraph 3.3  
181 As filed AGCTGTTCAATCTGG 195 196 210 211 225 226 240 241 255 256 270  
Amended AGCTGTTCAATCTGG AATCTTCCAAAATCG AAGTTATCCTGAAGA ATGCTATCGTATACA ACTCTATGTACGAAA ACTTCTCCACCTCCT 267  
Fig.1 SI#1 AGCTGTTCAATCTGG AATCTTCCAAAATCG AAGTTATCCTGAAGA ATGCTATCGTATACA ACTCTATGTACGAAA ACTTCTCCACCTCCT 267  
Fig.3 SI#5 AGCTGTTCAATCTGG AATCTTCCAAAATCG AAGTTATCCTGAAGA ATGCTATCGTATACA ACTCTATGTACGAAA ACTTCTCCACCTCCT 268  
Fig.2 SI#3 AGCTGTTCAATCTGG AATCTTCCAAAATCG AAGTTATCCTGAAGA ATGCTATCGTATACA ACTCTATGTACGAAA ACTTCTCCACCTCCT 262  
259

Paragraph 3.4  
271 As filed TCTGGATCCGTATCC 285 286 300 301 315 316 330 331 345 346 360  
Amended TCTGGATCCGTATCC CAAAATACTTCAACT CCATCTCTCTGAACA ATGAATACACCATCA TCAACTGCATGGAAA ACAATTCTGGTTGGA 356  
Fig.1 SI#1 TCTGGATCCGTATCC CAAAATACTTCAACT CCATCTCTCTGAACA ATGAATACACCATCA TCAACTGCATGGAAA ACAATTCTGGTTGGA 357  
Fig.3 SI#5 TCTGGATCCGTATCC CAAAATACTTCAACT CCATCTCTCTGAACA ATGAATACACCATCA TCAACTGCATGGAAA ACAATTCTGGTTGGA 358  
Fig.2 SI#3 TCTGGATCCGTATCC CAAAATACTTCAACT CCATCTCTCTGAACA ATGAATACACCATCA TCAACTGCATGGAAA ACAATTCTGGTTGGA 352  
349

Paragraph 3.5  
361 As filed AAGTATCTCTGAACT 375 376 390 391 405 406 420 421 435 436 450  
Amended AAGTATCTCTGAACT ACGGTGAAATCATCT GGACTCTGCAGGACA CTCAGGAAATCAAAC AGCGTGTGTATTCA AATACTCTCAGATGA 446  
Fig.1 SI#1 AAGTATCTCTGAACT ACGGTGAAATCATCT GGACTCTGCAGGACA CTCAGGAAATCAAAC AGCGTGTGTATTCA AATACTCTCAGATGA 447  
Fig.3 SI#5 AAGTATCTCTGAACT ACGGTGAAATCATCT GGACTCTGCAGGACA CTCAGGAAATCAAAC AGCGTGTGTATTCA AATACTCTCAGATGA 448  
Fig.2 SI#3 AAGTATCTCTGAACT ACGGTGAAATCATCT GGACTCTGCAGGACA CTCAGGAAATCAAAC AGCGTGTGTATTCA AATACTCTCAGATGA 442  
439

Paragraph 3.6  
451 As filed TCAACATCTCTGACT 465 466 480 481 495 496 510 511 525 526 540  
Amended TCAACATCTCTGACT ACATCAATCGTGGA TCTTCGTTACCATCA CCAACAATCGTCTGA ATAACTCCAAAATCT ACATCAACGCGCGTC 535  
Fig.1 SI#1 TCAACATCTCTGACT ACATCAATCGTGGA TCTTCGTTACCATCA CCAACAATCGTCTGA ATAACTCCAAAATCT ACATCAACGCGCGTC 537  
Fig.3 SI#5 TCAACATCTCTGACT ACATCAATCGTGGA TCTTCGTTACCATCA CCAACAATCGTCTGA ATAACTCCAAAATCT ACATCAACGCGCGTC 538  
Fig.2 SI#3 TCAACATCTCTGACT ACATCAATCGTGGA TCTTCGTTACCATCA CCAACAATCGTCTGA ATAACTCCAAAATCT ACATCAACGCGCGTC 532  
529

Paragraph 3.7

541 555 556 570 571 585 586 600 601 615 616 630 624  
As filed TGATCGACCAGAAAC CGATCTCCAATCTGG GTAACATCCACGTTT CTAATAACATCATGT TCAAACTGGACGGTT GTCGTGACACTCACC  
Amended TGATCGACCAGAAAC CGATCTCCAATCTGG GTAACATCCACGTTT CTAATAACATCATGT TCAAACTGGACGGTT GTCGTGACACTCACC  
Fig. 1 SI#1 TGATCGACCAGAAAC CGATCTCCAATCTGG GTAACATCCACGTTT CTAATAACATCATGT TCAAACTGGACGGTT GTCGTGACACTCACC  
Fig. 3 SI#5 TGATCGACCAGAAAC CGATCTCCAATCTGG GTAACATCCACGTTT CTAATAACATCATGT TCAAACTGGACGGTT GTCGTGACACTCACC  
Fig. 2 SI#3 TGATCGACCAGAAAC CGATCTCCAATCTGG GTAACATCCACGTTT CTAATAACATCATGT TCAAACTGGACGGTT GTCGTGACACTCACC

Paragraph 3.8

631 645 646 660 661 675 676 690 691 705 706 720 714  
As filed GCTACATCTGGATCA AATACCTCAATCTGT TCGACAAAGAACTGA ACGAAAAGAAATCA AAGACCTGTACGACA ACCAGTCCAATTCTG  
Amended GCTACATCTGGATCA AATACCTCAATCTGT TCGACAAAGAACTGA ACGAAAAGAAATCA AAGACCTGTACGACA ACCAGTCCAATTCTG  
Fig. 1 SI#1 GCTACATCTGGATCA AATACCTCAATCTGT TCGACAAAGAACTGA ACGAAAAGAAATCA AAGACCTGTACGACA ACCAGTCCAATTCTG  
Fig. 3 SI#5 GCTACATCTGGATCA AATACCTCAATCTGT TCGACAAAGAACTGA ACGAAAAGAAATCA AAGACCTGTACGACA ACCAGTCCAATTCTG  
Fig. 2 SI#3 GCTACATCTGGATCA AATACCTCAATCTGT TCGACAAAGAACTGA ACGAAAAGAAATCA AAGACCTGTACGACA ACCAGTCCAATTCTG

Paragraph 3.9

721 735 736 750 751 765 766 780 781 795 796 810 804  
As filed GTATCCTGAAAGACT TCTGGGTGACTACC TGCAGTACGACAAAC CGTACTACATGCTGA ATCTGTACGATCCGA ACAATACGTTGACG  
Amended GTATCCTGAAAGACT TCTGGGTGACTACC TGCAGTACGACAAAC CGTACTACATGCTGA ATCTGTACGATCCGA ACAATACGTTGACG  
Fig. 1 SI#1 GTATCCTGAAAGACT TCTGGGTGACTACC TGCAGTACGACAAAC CGTACTACATGCTGA ATCTGTACGATCCGA ACAATACGTTGACG  
Fig. 3 SI#5 GTATCCTGAAAGACT TCTGGGTGACTACC TGCAGTACGACAAAC CGTACTACATGCTGA ATCTGTACGATCCGA ACAATACGTTGACG  
Fig. 2 SI#3 GTATCCTGAAAGACT TCTGGGTGACTACC TGCAGTACGACAAAC CGTACTACATGCTGA ATCTGTACGATCCGA ACAATACGTTGACG

Paragraph 3.10

811 825 826 840 841 855 856 870 871 885 886 900 894  
As filed TCAACAATGTAGGTA TCCGCGGTACATGT ACCTGAAAGGTCCGC GTGGTCTGTTATGA CTACCAACATCTACC TGAACCTCTCCCTGT  
Amended TCAACAATGTAGGTA TCCGCGGTACATGT ACCTGAAAGGTCCGC GTGGTCTGTTATGA CTACCAACATCTACC TGAACCTCTCCCTGT  
Fig. 1 SI#1 TCAACAATGTAGGTA TCCGCGGTACATGT ACCTGAAAGGTCCGC GTGGTCTGTTATGA CTACCAACATCTACC TGAACCTCTCCCTGT  
Fig. 3 SI#5 TCAACAATGTAGGTA TCCGCGGTACATGT ACCTGAAAGGTCCGC GTGGTCTGTTATGA CTACCAACATCTACC TGAACCTCTCCCTGT  
Fig. 2 SI#3 TCAACAATGTAGGTA TCCGCGGTACATGT ACCTGAAAGGTCCGC GTGGTCTGTTATGA CTACCAACATCTACC TGAACCTCTCCCTGT

Paragraph 3.11

901 915 916 930 931 945 946 960 961 975 976 990 981  
As filed ACCGTGGTACCAAT TCATCATCAAGAAAT ACGCGTCTGGTAACA AGGACAATATD C GCAACAATGATCGTG TATACATCAATGTTG  
Amended ACCGTGGTACCAAT TCATCATCAAGAAAT ACGCGTCTGGTAACA AGGACAATATCGTTC GCAACAATGATCGTG TATACATCAATGTTG  
Fig. 1 SI#1 ACCGTGGTACCAAT TCATCATCAAGAAAT ACGCGTCTGGTAACA AGGACAATATCGTTC GCAACAATGATCGTG TATACATCAATGTTG  
Fig. 3 SI#5 ACCGTGGTACCAAT TCATCATCAAGAAAT ACGCGTCTGGTAACA AGGACAATATCGTTC GCAACAATGATCGTG TATACATCAATGTTG  
Fig. 2 SI#3 ACCGTGGTACCAAT TCATCATCAAGAAAT ACGCGTCTGGTAACA AGGACAATATCGTTC GCAACAATGATCGTG TATACATCAATGTTG

Paragraph 3.12

991 1005 1006 1020 1021 1035 1036 1050 1051 1065 1066 1080 1071  
As filed TAGTTAAGAACAAG AATACCGTCTGGCTA CCAATGCTTCTCAGG CTGGTGTAGAAAAGA TCCTGTCTGCTCTGG AATCCCGGACGTTG  
Amended TAGTTAAGAACAAG AATACCGTCTGGCTA CCAATGCTTCTCAGG CTGGTGTAGAAAAGA TCCTGTCTGCTCTGG AATCCCGGACGTTG 1077  
Fig.1 SI#1 TAGTTAAGAACAAG AATACCGTCTGGCTA CCAATGCTTCTCAGG CTGGTGTAGAAAAGA TCCTGTCTGCTCTGG AATCCCGGACGTTG 1078  
Fig.3 SI#5 TAGTTAAGAACAAG AATACCGTCTGGCTA CCAATGCTTCTCAGG CTGGTGTAGAAAAGA TCCTGTCTGCTCTGG AATCCCGGACGTTG 1072  
Fig.2 SI#3 TAGTTAAGAACAAG AATACCGTCTGGCTA CCAATGCTTCTCAGG CTGGTGTAGAAAAGA TCCTGTCTGCTCTGG AATCCCGGACGTTG 1069

Paragraph 3.13

1081 1095 1096 1110 1111 1125 1126 1140 1141 1155 1156 1170 1161  
As filed GTAATCTGTCTCAGG TAGTTGTAATGAAAT CCAAGAACGACCAGG GTATCACTAACAAAT GCAAAATGAATCTGC AGGACAACAATGGTA  
Amended GTAATCTGTCTCAGG TAGTTGTAATGAAAT CCAAGAACGACCAGG GTATCACTAACAAAT GCAAAATGAATCTGC AGGACAACAATGGTA 1167  
Fig.1 SI#1 GTAATCTGTCTCAGG TAGTTGTAATGAAAT CCAAGAACGACCAGG GTATCACTAACAAAT GCAAAATGAATCTGC AGGACAACAATGGTA 1168  
Fig.3 SI#5 GTAATCTGTCTCAGG TAGTTGTAATGAAAT CCAAGAACGACCAGG GTATCACTAACAAAT GCAAAATGAATCTGC AGGACAACAATGGTA 1162  
Fig.2 SI#3 GTAATCTGTCTCAGG TAGTTGTAATGAAAT CCAAGAACGACCAGG GTATCACTAACAAAT GCAAAATGAATCTGC AGGACAACAATGGTA 1159

Paragraph 3.14

1171 1185 1186 1200 1201 1215 1216 1230 1231 1245 1246 1260 1251  
As filed ACGATATCGGTTTCA TCGGTTTCCACCAGT TCAACAATATCGCTA AACTGGTTGCTTCCA ACTGGTACAATCGTC AGATCGAAACGTTCTCT  
Amended ACGATATCGGTTTCA TCGGTTTCCACCAGT TCAACAATATCGCTA AACTGGTTGCTTCCA ACTGGTACAATCGTC AGATCGAAACGTTCTCT 1257  
Fig.1 SI#1 ACGATATCGGTTTCA TCGGTTTCCACCAGT TCAACAATATCGCTA AACTGGTTGCTTCCA ACTGGTACAATCGTC AGATCGAAACGTTCTCT 1258  
Fig.3 SI#5 ACGATATCGGTTTCA TCGGTTTCCACCAGT TCAACAATATCGCTA AACTGGTTGCTTCCA ACTGGTACAATCGTC AGATCGAAACGTTCTCT 1252  
Fig.2 SI#3 ACGATATCGGTTTCA TCGGTTTCCACCAGT TCAACAATATCGCTA AACTGGTTGCTTCCA ACTGGTACAATCGTC AGATCGAAACGTTCTCT 1249

Paragraph 3.15

1261 1275 1276 1290 1291 1305 1306 1320 1321 1335 1336 1350 1332  
As filed CTCGCACCTCTGGTT GCTCTTGGGAGTTCA TCCCGGTTGATGACG GTTGGGGTGAACGTC CGCTGTAACCCGGGA AAGCTT  
Amended CTCGCACCTCTGGTT GCTCTTGGGAGTTCA TCCCGGTTGATGACG GTTGGGGTGAACGTC CGCTGTAACCCGGGA AAGCTT 1338  
Fig.1 SI#1 CTCGCACCTCTGGTT GCTCTTGGGAGTTCA TCCCGGTTGATGACG GTTGGGGTGAACGTC CGCTGTAACCCGGGA AAGCTT 1332  
Fig.3 SI#5 CTCGCACCTCTGGTT GCTCTTGGGAGTTCA TCCCGGTTGATGACG GTTGGGGTGAACGTC CGCTGTAACCCGGGA AAGCTT 1326  
Fig.2 SI#3 CTCGCACCTCTGGTT GCTCTTGGGAGTTCA TCCCGGTTGATGACG GTTGGGGTGAACGTC CGCTGTAACCCGGGA AAGCTT 1323

Alignment 4

SEQ ID NO:40 (appearing on page 38 in the specification as filed) has been amended as follows:

- At position 121 of paragraph 4.2, T→I.
- At position 327 of paragraph 4.4, Q→W.
- At position 334 of paragraph 4.4, K→Y.

Paragraph 4.1

1	15	16	30	31	45	46	60	61	75	76	90
As filed	-FNKYNSEILNNIIL	NLRYKDNLLIDL	SGY	GAKVEVYDGV	ELNDK	NQFKLTSS	ANSKIRV	TQNQNIIFNS	VFLDF	SVSFWIRIPKYKNDG	89
Amended	-FNKYNSEILNNIIL	NLRYKDNLLIDL	SGY	GAKVEVYDGV	ELNDK	NQFKLTSS	ANSKIRV	TQNQNIIFNS	VFLDF	SVSFWIRIPKYKNDG	89
Fig 4 SI#8	MANKYNSEILNNIIL	NLRYKDNLLIDL	SGY	GAKVEVYDGV	ELNDK	NQFKLTSS	ANSKIRV	TQNQNIIFNS	VFLDF	SVSFWIRIPKYKNDG	90
Ac# M81186	MFNKYNSEILNNIIL	NLRYKDNLLIDL	SGY	GAKVEVYDGV	ELNDK	NQFKLTSS	ANSKIRV	TQNQNIIFNS	VFLDF	SVSFWIRIPKYKNDG	90

Paragraph 4.2

91	105	106	120	121	135	136	150	151	165	166	180
As filed	IQNYIHNEYTIINCM	KNSGWKISIRGNRI	IWTLIDINGKTSVF	FEYNIRE	DISEYINR	WFFVTITNNL	NNAKI	YINGKLESNT	DIKDI	179	
Amended	IQNYIHNEYTIINCM	KNSGWKISIRGNRI	IWTLIDINGKTSVF	FEYNIRE	DISEYINR	WFFVTITNNL	NNAKI	YINGKLESNT	DIKDI	179	
Fig 4 SI#8	IQNYIHNEYTIINCM	KNSGWKISIRGNRI	IWTLIDINGKTSVF	FEYNIRE	DISEYINR	WFFVTITNNL	NNAKI	YINGKLESNT	DIKDI	180	
Ac# M81186	IQNYIHNEYTIINCM	KNSGWKISIRGNRI	IWTLIDINGKTSVF	FEYNIRE	DISEYINR	WFFVTITNNL	NNAKI	YINGKLESNT	DIKDI	180	

Paragraph 4.3

181	195	196	210	211	225	226	240	241	255	256	270
As filed	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQSNIEERYK	IQSYEYLKDF	WGNP	LMYNKEYYMFNAGNK	NSYIKLKD	SPVGEI	269		
Amended	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQSNIEERYK	IQSYEYLKDF	WGNP	LMYNKEYYMFNAGNK	NSYIKLKD	SPVGEI	269		
Fig 4 SI#8	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQSNIEERYK	IQSYEYLKDF	WGNP	LMYNKEYYMFNAGNK	NSYIKLKD	SPVGEI	270		
Ac# M81186	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQSNIEERYK	IQSYEYLKDF	WGNP	LMYNKEYYMFNAGNK	NSYIKLKD	SPVGEI	270		

Paragraph 4.4

271 285 286 300 301 315 316 330 331 345 346 360  
As filed LTRSKYNQNSKYINY RDLYIGKEKFIIRKKS NSQSINDDIVRKEDY IYLDFFNLNOEWRVY TYKPFKKEEKLFLA PISDSDEFYNTIQIK 359  
Amended LTRSKYNQNSKYINY RDLYIGKEKFIIRKKS NSQSINDDIVRKEDY IYLDFFNLNOEWRVY TYKPFKKEEKLFLA PISDSDEFYNTIQIK 359  
Fig. 4 SI#8 LTRSKYNQNSKYINY RDLYIGKEKFIIRKKS NSQSINDDIVRKEDY IYLDFFNLNOEWRVY TYKPFKKEEKLFLA PISDSDEFYNTIQIK 360  
Ac# M81186 LTRSKYNQNSKYINY RDLYIGKEKFIIRKKS NSQSINDDIVRKEDY IYLDFFNLNOEWRVY TYKPFKKEEKLFLA PISDSDEFYNTIQIK 360

Paragraph 4.5

361 375 376 390 391 405 406 420 421 435 436 450  
As filed EYDEQPTYSCQLLFFK KDEESTDEIGLIGIH RFYESGIVFEEYKDY FCISKWYLKEVKRKP YNLKLGCNWQFIPKD EGWTE 439  
Amended EYDEQPTYSCQLLFFK KDEESTDEIGLIGIH RFYESGIVFEEYKDY FCISKWYLKEVKRKP YNLKLGCNWQFIPKD EGWTE 439  
Fig 4 SI#8 EYDEQPTYSCQLLFFK KDEESTDEIGLIGIH RFYESGIVFEEYKDY FCISKWYLKEVKRKP YNLKLGCNWQFIPKD EGWTE 440  
Ac# M81186 EYDEQPTYSCQLLFFK KDEESTDEIGLIGIH RFYESGIVFEEYKDY FCISKWYLKEVKRKP YNLKLGCNWQFIPKD EGWTE 440

Alignment 5

SEQ ID NO:39 (appearing on page 39 in the specification as filed) has been amended as follows:

- At positions 15-17 of paragraph 5.1, TTT is deleted;
- At position 820 of paragraph 5.10, A is inserted;
- At position 933 of paragraph 5.11, T is inserted;
- At position 988 of paragraph 5.11, G is inserted; and
- At position 1226 of paragraph 5.14, A is inserted.



SEQ ID NO:7 (appearing in Figure 4 of the specification as filed) has been amended as follows:

- At position 255 of paragraph 5.3, T→C.

Paragraph 5.1

Fig 4 as filed  
 GAATTACGATGGC- --CAACAAATACAAT TCCGAAATCCTGAAC AATATCATCCTGAAC CTGCGTTACAAAGAC AACAAATCTGATCGAT 90  
 Fig4 corrected GAATTACGATGGC- --CAACAAATACAAT TCCGAAATCCTGAAC AATATCATCCTGAAC CTGCGTTACAAAGAC AACAAATCTGATCGAT 87  
 P.39 corrected -----ATGGC CAACAAATACAAT TCCGAAATCCTGAAC AATATCATCCTGAAC CTGCGTTACAAAGAC AACAAATCTGATCGAT 78  
 P.39 as filed -----ATGGC CAACAAATACAAT TCCGAAATCCTGAAC AATATCATCCTGAAC CTGCGTTACAAAGAC AACAAATCTGATCGAT 81

Paragraph 5.2

Fig 4 as filed  
 CTGTCTGGTTACGGT GCTAAAGTTGAAGTA TACGACGGTGTGAA CTGAAATGACAAGAAC CAGTTCAAACGTGACC TCTTCCGCTAACTCT 180  
 Fig4 corrected CTGTCTGGTTACGGT GCTAAAGTTGAAGTA TACGACGGTGTGAA CTGAAATGACAAGAAC CAGTTCAAACGTGACC TCTTCCGCTAACTCT 177  
 P.39 corrected CTGTCTGGTTACGGT GCTAAAGTTGAAGTA TACGACGGTGTGAA CTGAAATGACAAGAAC CAGTTCAAACGTGACC TCTTCCGCTAACTCT 168  
 P.39 as filed CTGTCTGGTTACGGT GCTAAAGTTGAAGTA TACGACGGTGTGAA CTGAAATGACAAGAAC CAGTTCAAACGTGACC TCTTCCGCTAACTCT 171

Paragraph 5.3

Fig 4 as filed  
 AAGATCCGTTGTTACT CAGAATCAGAACATC ATCTTCAACTCCGTA TTCTTGGACTTCTCT GTTTCCTTCTGGATCGTATCCCGAAATAC 270  
 Fig4 corrected AAGATCCGTTGTTACT CAGAATCAGAACATC ATCTTCAACTCCGTA TTCTTGGACTTCTCT GTTTCCTTCTGGATCGTATCCCGAAATAC 267  
 P.39 corrected AAGATCCGTTGTTACT CAGAATCAGAACATC ATCTTCAACTCCGTA TTCTTGGACTTCTCT GTTTCCTTCTGGATCGTATCCCGAAATAC 258  
 P.39 as filed AAGATCCGTTGTTACT CAGAATCAGAACATC ATCTTCAACTCCGTA TTCTTGGACTTCTCT GTTTCCTTCTGGATCGTATCCCGAAATAC 261

Paragraph 5.4

Fig 4 as filed  
 AAGAACGACGGTATC CAGAATTACATCCAC AATGAATACACCATC ATCAACTGCATGAAG AATAACTCTGGTTGG AAGATCTCCATCCGC 360  
 Fig4 corrected AAGAACGACGGTATC CAGAATTACATCCAC AATGAATACACCATC ATCAACTGCATGAAG AATAACTCTGGTTGG AAGATCTCCATCCGC 357  
 P.39 corrected AAGAACGACGGTATC CAGAATTACATCCAC AATGAATACACCATC ATCAACTGCATGAAG AATAACTCTGGTTGG AAGATCTCCATCCGC 348  
 P.39 as filed AAGAACGACGGTATC CAGAATTACATCCAC AATGAATACACCATC ATCAACTGCATGAAG AATAACTCTGGTTGG AAGATCTCCATCCGC 351

Paragraph 5.5

Fig 4 as filed 361 375 376 390 391 405 406 420 421 435 436 450 447  
 Fig4 corrected GGTAACCGGTATCATC TGGACTCTGTATCGAT ATCAACGGTAAGACC AAATCTGTATTCTTC GAATACAACATCCGT GAAGACATCTCTGAA 447  
 P.39 corrected GGTAACCGGTATCATC TGGACTCTGTATCGAT ATCAACGGTAAGACC AAATCTGTATTCTTC GAATACAACATCCGT GAAGACATCTCTGAA 447  
 P.39 as filed GGTAACCGGTATCATC TGGACTCTGTATCGAT ATCAACGGTAAGACC AAATCTGTATTCTTC GAATACAACATCCGT GAAGACATCTCTGAA 441

Paragraph 5.6

Fig 4 as filed 451 465 466 480 481 495 496 510 511 525 526 540 537  
 Fig4 corrected TACATCAATCGCTGG TTCTTCGTTACCATC ACCAATAACCTGAAC AATGCTAAAATCTAC ATCAACGGTAAACTG GAATCTAATACCGAC 537  
 P.39 corrected TACATCAATCGCTGG TTCTTCGTTACCATC ACCAATAACCTGAAC AATGCTAAAATCTAC ATCAACGGTAAACTG GAATCTAATACCGAC 537  
 P.39 as filed TACATCAATCGCTGG TTCTTCGTTACCATC ACCAATAACCTGAAC AATGCTAAAATCTAC ATCAACGGTAAACTG GAATCTAATACCGAC 528  
 531

Paragraph 5.7

Fig 4 as filed 541 555 556 570 571 585 586 600 601 615 616 630 627  
 Fig4 corrected ATCAAAGACATCCGT GAAGTTATCGCTAAC GGTGAAATCATCTTC AAACCTGGACGGTGAC ATCGATCGTACCCAG TTCATCTGGATGAAA 627  
 P.39 corrected ATCAAAGACATCCGT GAAGTTATCGCTAAC GGTGAAATCATCTTC AAACCTGGACGGTGAC ATCGATCGTACCCAG TTCATCTGGATGAAA 627  
 P.39 as filed ATCAAAGACATCCGT GAAGTTATCGCTAAC GGTGAAATCATCTTC AAACCTGGACGGTGAC ATCGATCGTACCCAG TTCATCTGGATGAAA 618  
 621

Paragraph 5.8

Fig 4 as filed 631 645 646 660 661 675 676 690 691 705 706 720 717  
 Fig4 corrected TACTTCTCCATCTTC AACACCGAACTGTCT CAGTCCAATATCGAA GAACGGTACAAGATC CAGTCTTACTCCGAA TACCTGAAAAGACTTC 717  
 P.39 corrected TACTTCTCCATCTTC AACACCGAACTGTCT CAGTCCAATATCGAA GAACGGTACAAGATC CAGTCTTACTCCGAA TACCTGAAAAGACTTC 717  
 P.39 as filed TACTTCTCCATCTTC AACACCGAACTGTCT CAGTCCAATATCGAA GAACGGTACAAGATC CAGTCTTACTCCGAA TACCTGAAAAGACTTC 708  
 711

Paragraph 5.9

Fig 4 as filed 721 735 736 750 751 765 766 780 781 795 796 810 807  
 Fig4 corrected TGGGGTAATCCGCTG ATGTACAACAAGAA TACTATATGTTCAT GCTGGTAACAAGAAC TCCTACATCAAACTG AAGAAAAGACTCTCCG 807  
 P.39 corrected TGGGGTAATCCGCTG ATGTACAACAAGAA TACTATATGTTCAT GCTGGTAACAAGAAC TCCTACATCAAACTG AAGAAAAGACTCTCCG 807  
 P.39 as filed TGGGGTAATCCGCTG ATGTACAACAAGAA TACTATATGTTCAT GCTGGTAACAAGAAC TCCTACATCAAACTG AAGAAAAGACTCTCCG 798  
 801

Paragraph 5.10

Fig 4 as filed 811 825 826 840 841 855 856 870 871 885 886 900 897  
 Fig4 corrected GTTGGTGAATCCTG ACTCGTTCCAAATAC AACAGAACTCTAAA TACATCAACTACCGC GACCTGTACATCGGT GAAAAGTTTCATCATC 897  
 P.39 corrected GTTGGTGAATCCTG ACTCGTTCCAAATAC AACAGAACTCTAAA TACATCAACTACCGC GACCTGTACATCGGT GAAAAGTTTCATCATC 897  
 P.39 as filed GTTGGTGAATCCTG ACTCGTTCCAAATAC AACAGAACTCTAAA TACATCAACTACCGC GACCTGTACATCGGT GAAAAGTTTCATCATC 888  
 890

Paragraph 5.11

Fig 4 as filed 901 915 916 930 931 945 946 960 961 975 976 990 997  
 Fig4 corrected CGTCGCAAAATCTAAC TCTCAGTCCATCAAT GATGACATCGTACGT AAAGAAGACTACATC TACCTGGACTTCTTC AACCTGAATCAGGAA 997  
 P.39 corrected CGTCGCAAAATCTAAC TCTCAGTCCATCAAT GATGACATCGTACGT AAAGAAGACTACATC TACCTGGACTTCTTC AACCTGAATCAGGAA 997  
 P.39 as filed CGTCGCAAAATCTAAC TCTCAGTCCATCAAT GATGACATCGTACGT AAAGAAGACTACATC TACCTGGACTTCTTC AACCTGAATCAGGAA 978  
 978

Paragraph 5.12

Fig 4 as filed 991 1005 1006 1020 1021 1035 1036 1050 1051 1065 1066 1080 1077  
 Fig4 corrected TGGCGTGTATACACC TACAAGTACTTCAAG AAAGAAGAAAGAAAG CTTTCTCTGGTCCG ATCTCTGATTTCCGAC GAACTCTACAACACC 1077  
 P.39 corrected TGGCGTGTATACACC TACAAGTACTTCAAG AAAGAAGAAAGAAAG CTTTCTCTGGTCCG ATCTCTGATTTCCGAC GAACTCTACAACACC 1077  
 P.39 as filed TGGCGTGTATACACC TACAAGTACTTCAAG AAAGAAGAAAGAAAG CTTTCTCTGGTCCG ATCTCTGATTTCCGAC GAACTCTACAACACC 1068  
 1068

Paragraph 5.13

Fig 4 as filed 1081 1095 1096 1110 1111 1125 1126 1140 1141 1155 1156 1170 1167  
 Fig4 corrected ATCCAGATCAAAGAA TACGACGAACAGCCG ACCTACTCTTGCCAG CTGCTGTTCAAGAA GATGAAGAATCTACT GACGAAATCGGTCTG 1167  
 P.39 corrected ATCCAGATCAAAGAA TACGACGAACAGCCG ACCTACTCTTGCCAG CTGCTGTTCAAGAA GATGAAGAATCTACT GACGAAATCGGTCTG 1167  
 P.39 as filed ATCCAGATCAAAGAA TACGACGAACAGCCG ACCTACTCTTGCCAG CTGCTGTTCAAGAA GATGAAGAATCTACT GACGAAATCGGTCTG 1158  
 1158

Paragraph 5.14

Fig 4 as filed 1171 1185 1186 1200 1201 1215 1216 1230 1231 1245 1246 1260 1257  
 Fig4 corrected ATCGGTATCCACCGT TTCTACGAATCTGGT ATCGTATTCGAAGAA TACAAAGACTACTTC TGCATCTCCAAATGG TACCTGAAGGAAGTT 1257  
 P.39 corrected ATCGGTATCCACCGT TTCTACGAATCTGGT ATCGTATTCGAAGAA TACAAAGACTACTTC TGCATCTCCAAATGG TACCTGAAGGAAGTT 1257  
 P.39 as filed ATCGGTATCCACCGT TTCTACGAATCTGGT ATCGTATTCGAAGAA TACAAAGACTACTTC TGCATCTCCAAATGG TACCTGAAGGAAGTT 1248  
 1247

Paragraph 5.10

811 825 826 811 825 826 840 841 855 856 870 871 885 886 900  
Fig 4 as filed GTTGGTGAATCCTG ACTCGTTCCAAATAC AACGAGAATCTAAA TACATCAACTACCGC GACCTGTACATCGGT GAAAAGTTTCATCATC 897  
Fig4 corrected GTTGGTGAATCCTG ACTCGTTCCAAATAC AACGAGAATCTAAA TACATCAACTACCGC GACCTGTACATCGGT GAAAAGTTTCATCATC 897  
P.39 corrected GTTGGTGAATCCTG ACTCGTTCCAAATAC AACGAGAATCTAAA TACATCAACTACCGC GACCTGTACATCGGT GAAAAGTTTCATCATC 888  
P.39 as filed GTTGGTGAATCCTG ACTCGTTCCAAATAC AACGAGAATCTAAA TACATCAACTACCGC GACCTGTACATCGGT GAAAAGTTTCATCATC 890

Paragraph 5.11

901 915 916 915 916 930 931 945 946 960 961 975 976 990  
Fig 4 as filed CGTCGCAAAATCTAAC TCTCAGTCCATCAAT GATGACATCGTACGT AAAGAAGACTACATC TACCTGGACTTCTTC AACCTGAATCAGGAA 987  
Fig4 corrected CGTCGCAAAATCTAAC TCTCAGTCCATCAAT GATGACATCGTACGT AAAGAAGACTACATC TACCTGGACTTCTTC AACCTGAATCAGGAA 987  
P.39 corrected CGTCGCAAAATCTAAC TCTCAGTCCATCAAT GATGACATCGTACGT AAAGAAGACTACATC TACCTGGACTTCTTC AACCTGAATCAGGAA 978  
P.39 as filed CGTCGCAAAATCTAAC TCTCAGTCCATCAAT GATGACATCGTACGT AAAGAAGACTACATC TACCTGGACTTCTTC AACCTGAATCAGGAA 978

Paragraph 5.12

991 1005 1006 1005 1006 1020 1021 1035 1036 1050 1051 1065 1066 1080  
Fig 4 as filed TGGCGTGTATACACC TACAAGTACTTCAAG AAAGAAGAAAGAAAG CTTTTCCTGGCTCCG ATCTCTGATTTCCGAC GAACTCTACAACACC 1077  
Fig4 corrected TGGCGTGTATACACC TACAAGTACTTCAAG AAAGAAGAAAGAAAG CTTTTCCTGGCTCCG ATCTCTGATTTCCGAC GAACTCTACAACACC 1077  
P.39 corrected TGGCGTGTATACACC TACAAGTACTTCAAG AAAGAAGAAAGAAAG CTTTTCCTGGCTCCG ATCTCTGATTTCCGAC GAACTCTACAACACC 1068  
P.39 as filed TGGCGTGTATACACC TACAAGTACTTCAAG AAAGAAGAAAGAAAG CTTTTCCTGGCTCCG ATCTCTGATTTCCGAC GAACTCTACAACACC 1068

Paragraph 5.13

1081 1095 1096 1095 1096 1110 1111 1125 1126 1140 1141 1155 1156 1170  
Fig 4 as filed ATCCAGATCAAAGAA TACGACGAACAGCCG ACCTACTCTTGCCAG CTGCTGTTCAAGAA GATGAAGAATCTACT GACGAAATCGGTCTG 1167  
Fig4 corrected ATCCAGATCAAAGAA TACGACGAACAGCCG ACCTACTCTTGCCAG CTGCTGTTCAAGAA GATGAAGAATCTACT GACGAAATCGGTCTG 1167  
P.39 corrected ATCCAGATCAAAGAA TACGACGAACAGCCG ACCTACTCTTGCCAG CTGCTGTTCAAGAA GATGAAGAATCTACT GACGAAATCGGTCTG 1158  
P.39 as filed ATCCAGATCAAAGAA TACGACGAACAGCCG ACCTACTCTTGCCAG CTGCTGTTCAAGAA GATGAAGAATCTACT GACGAAATCGGTCTG 1158

Paragraph 5.14

1171 1185 1186 1171 1185 1186 1200 1201 1215 1216 1230 1231 1245 1246 1260  
Fig 4 as filed ATCGGTATCCACCGT TTCTACGAATCTGGT ATCGTATTCGAAGAA TACAAGACTTACTTC TGATCTCCAAATGG TACCTGAAGGAAGTT 1257  
Fig4 corrected ATCGGTATCCACCGT TTCTACGAATCTGGT ATCGTATTCGAAGAA TACAAGACTTACTTC TGATCTCCAAATGG TACCTGAAGGAAGTT 1257  
P.39 corrected ATCGGTATCCACCGT TTCTACGAATCTGGT ATCGTATTCGAAGAA TACAAGACTTACTTC TGATCTCCAAATGG TACCTGAAGGAAGTT 1248  
P.39 as filed ATCGGTATCCACCGT TTCTACGAATCTGGT ATCGTATTCGAAGAA TACAAGACTTACTTC TGATCTCCAAATGG TACCTGAAGGAAGTT 1247

Paragraph 5.15

1261 1275 1276 1290 1291 1305 1306 1320 1321 1335 1336 1350  
Fig 4 as filed AAACGCAAACCGTAC AACCTGAAACTGGGT TGCAATTGGCAGTTC ATCCCGAAAGACGAA GGTGGACCGAATAG TAAGAATTC----- 1341  
Fig4 corrected AAACGCAAACCGTAC AACCTGAAACTGGGT TGCAATTGGCAGTTC ATCCCGAAAGACGAA GGTGGACCGAATAG TAAGAATTC----- 1341  
P.39 corrected AAACGCAAACCGTAC AACCTGAAACTGGGT TGCAATTGGCAGTTC ATCCCGAAAGACGAA GGTGGACCGAATAG TAACCTCTAGAGTCG 1338  
P.39 as filed AAACGCAAACCGTAC AACCTGAAACTGGGT TGCAATTGGCAGTTC ATCCCGAAAGACGAA GGTGGACCGAATAG TAACCTCTAGAGTCG 1337

Paragraph 5.16

1351 1365 1366 1380 1381 1395 1396 1410 1411 1425 1426 1440  
Fig 4 as filed ----- 1341  
Fig4 corrected ----- 1341  
P.39 corrected AGGCCTGCAG 1348  
P.39 as filed AGGCCTGCAG 1347